



University  
of Glasgow

<https://theses.gla.ac.uk/>

Theses Digitisation:

<https://www.gla.ac.uk/myglasgow/research/enlighten/theses/digitisation/>

This is a digitised version of the original print thesis.

Copyright and moral rights for this work are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This work cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

Enlighten: Theses

<https://theses.gla.ac.uk/>  
[research-enlighten@glasgow.ac.uk](mailto:research-enlighten@glasgow.ac.uk)

T H E S I S

submitted to

THE UNIVERSITY OF GLASGOW

in fulfilment of the  
requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

by

EDWARD M. HOWELLS

Chemistry Department,  
The Royal College of Science and Technology,  
Glasgow.

JANUARY, 1962.

ProQuest Number: 10647832

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 10647832

Published by ProQuest LLC (2017). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code  
Microform Edition © ProQuest LLC.

ProQuest LLC.  
789 East Eisenhower Parkway  
P.O. Box 1346  
Ann Arbor, MI 48106 – 1346

STUDIES ON SYNTHETIC ROUTES  
TO PHENOLIC PHTHALIDES



### ACKNOWLEDGMENTS

The author wishes to express his sincere appreciation of the constant encouragement and stimulating advice given by Professor P. L. Pauson and by Dr. G. T. Newbold during the course of this work.

The author would also like to thank Dr. F. S. Spring, F.R.S., for the initial provision of research facilities, and the Department of Scientific and Industrial Research for the award of a maintenance grant.

---

## CONTENTS

	<u>Page</u>
SUMMARY . . . . .	i - iv
INTRODUCTION	
Occurrence of Phenolic Phthalides . . . . .	1
Chemistry of Cyclopaldic Acid and Cyclopolic Acid .	5
Chemistry of Gladiolic Acid and Dihydro- gladiolic Acid .	8
Keto-Lactol Tautomerism . . . . .	11
Total Syntheses of Gladiolic Acid and Related Compounds .	18
General Methods of Phthalide Synthesis . . .	21
Infrared Spectra of Phenolic Phthalides . . .	30
THEORETICAL	
General Objectives . . . . .	32
Synthesis of 5-Hydroxy-7-methoxyphthalide ..	33
Outline of Possible Routes to Cyclopaldic Acid .	40
Synthetic Routes to 7-Hydroxy-5-methoxy-6- methylphthalide	42
Synthetic Routes to 5-Hydroxy-7-methoxy-6- methylphthalide	49
Discussion of Infrared and Ultraviolet Spectral Data .	68

EXPERIMENTAL	...	...	...	...	...	...	75
BIBLIOGRAPHY	...	...	...	...	...	...	124
APPENDIX	...	...	...	...	...	...	V - X

### SUMMARY

A synthesis of 5-hydroxy-7-methoxyphthalide (LXVI) was developed in an effort to prove that compound identical with a phthalide isolated from Helichrysum Arenarium. The synthesis of 5,6-diformyl-4-hydroxy-2-methoxy-3-methylbenzoic acid (cyclopaldic acid) (VIII), a mould metabolic product occurring in P. cyclopium Westling, was attempted with a view to confirming the structure assigned to the compound from degradative studies on the natural product. In order that possible general synthetic routes to (VIII) might first be investigated using more easily available starting material, a synthesis of 5,6-diformyl-2-hydroxy-4-methoxy-3-methylbenzoic acid (isocyclopaldic acid), isomeric with (VIII), was initially attempted.

The synthesis of 5-hydroxy-7-methoxyphthalide (LXVI) was achieved from methyl 4-hydroxy-6-methoxy-2-methylbenzoate (methyl isoeverninate) (LXXI), which was in turn obtained from methyl acetoacetate and methyl crotonate by adaptation of a series of reactions reported in the literature. (LXXI), on photobromination yielded methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate (LXXIV), which on hydrolysis with aqueous dioxan gave

4-bromo-5-hydroxy-7-methoxyphthalide (LXXVI). Acetylation and catalytic hydrogenation yielded 5-acetoxy-7-methoxyphthalide (LXXVIII), which gave 5-hydroxy-7-methoxyphthalide (LXVI) on alkaline hydrolysis.

In the attempted synthesis of isocyclopaldic acid, ethyl 3,6-dimethyl-2-hydroxy-4-methoxybenzoate (ethyl rhizonate) (LXXXVI), obtainable by a slight adaptation of the previously reported synthesis, was photobrominated to yield ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII). On treatment with aqueous acetone, (LXXXVII) gave 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) in a low yield, which could not be improved by use of other methods of hydrolysis. Acetylation of both (LXXXVII) and (LXXXVIII) produced 7-acetoxy-6-acetoxymethyl-5-methoxyphthalide (XC). An attempt to obtain 7-hydroxy-5-methoxy-6-methylphthalide (LXXXI) by hydrogenation of (LXXXVIII) was unsuccessful.

In the synthetic route to cyclopaldic acid (VIII) initially envisaged, methyl 3,6-diethyl-4-hydroxy-2-methoxybenzoate (methyl isorhizonate) (XCVII) was a necessary intermediate. The shorter of the two previously reported methods of obtaining this compound was re-examined, but the product was isolated in a very low overall yield. Ethyl

isorhizonate (CII) was obtained more readily from ethyl 2,4-dihydroxy-6-methylbenzoate (ethyl orsellinate) (LXXXII). Formylation of (LXXXII) gave ethyl 2,4-dihydroxy-3-formyl-6-methylbenzoate (ethyl haematommate) (LXXXIII), hydrogenation of which yielded ethyl 2,4-dihydroxy-3,6-dimethylbenzoate (ethyl  $\beta$ -orcinol carboxylate) (LXXXIV). Protection of the more active hydroxyl group in the latter compound by carbonate formation, followed by methylation of the other, yielded ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-methoxyphenyl carbonate (CI), hydrolysis of which produced ethyl isorhizonate (CII). An alternative route to ethyl  $\beta$ -orcinol carboxylate (LXXXIV) from ethyl orsellinate involved the formation of ethyl 2,4-dihydroxy-3-dimethylaminomethyl-6-methylbenzoate (LXXXV) by the Mannich Reaction. Hydrogenation of (LXXXV) yielded ethyl  $\beta$ -orcinol carboxylate (LXXXIV).

Photobromination of ethyl isorhizonate (CII) yielded ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (CIII), hydrolysis of which with aqueous acetone gave 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV). Acetylation of both (CIII) and (CIV) produced 1-acetoxy-6-acetoxymethyl-7-methoxyphthalide (CVI) and platinum-catalysed hydrogenation of (CIV) furnished 5-hydroxy-7-methoxy-6-methylbenzoate (LXXX).

Benzoylation of ethyl isorhizonate (CII) yielded ethyl 4-benzoyloxy-3,6-dimethyl-2-methoxybenzoate (CX), which on

photobromination gave ethyl 4-benzoyloxy-3,6-di(bromomethyl)-2-methoxybenzoate (CXI). Aqueous acetone hydrolysis of (CXI) gave 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV), together with a little 5-benzoyloxy-6-hydroxymethyl-7-methoxyphthalide (CXII), itself readily convertible to (CIV).

Acetylation of methyl 2-benzoyloxy-3-formyl-4-hydroxy-6-methylbenzoate (XCV) gave methyl 2,4-diacetoxy-3-diacetoxy-methyl-6-methylbenzoate (CXIII). Benzoylation of (XCV) gave methyl 4-benzoyloxy-2-benzoyloxy-3-formyl-6-methylbenzoate (CXIV), the attempted reduction and debenzoylation of which to produce methyl 4-benzoyloxy-3,6-dimethyl-2-hydroxybenzoate (CXV) was unsuccessful.

An attempted synthesis of cyclopaldic acid (VIII) from 3,5-dihydroxybenzoic acid (CXVIII) necessitated the initial synthesis of 3,5-dihydroxybenzyl alcohol (CXIX). Attempted lithium aluminium hydride reduction of (CXVIII) and a number of its ester derivatives was unsuccessful. Also, attempts to demethylate 3,5-dimethoxybenzyl alcohol (CXXIV) failed to produce the desired product.

The influence of intramolecular hydrogen bonding on ortho-hydroxybenzoic acid esters and to a lesser extent on 7-hydroxyphthalides was observed by comparison of their infrared absorption spectra in the carbonyl region with those of orthomethoxy-benzoic acid esters and 7-methoxyphthalides respectively. Ultraviolet spectral data obtained were also briefly considered.

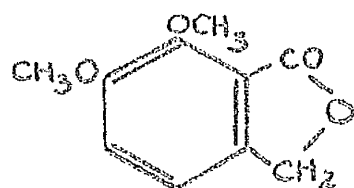
## I N T R O D U C T I O N



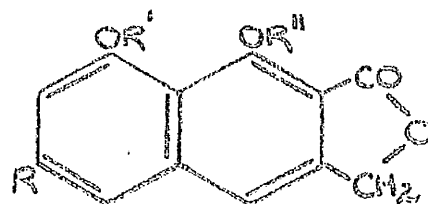
## Occurrence of Phenolic Phthalides

Substituted phthalides do not occur widely in nature, being found mainly in the lower forms of plant life, in lichens and in moulds.

Meconin (I), first isolated from opium seeds in 1832 by Couerbe, was structurally elucidated by the synthetic work of Fritsch.<sup>1</sup> Two phthalides,  $\alpha$ -sorigenin and  $\beta$ -sorigenin, isolated from the bark of Rhamnus japonica,<sup>2</sup> were formulated as naphthalene derivatives.<sup>3</sup> Their structures have recently been confirmed to be (II, R = OCH<sub>3</sub>, R' = R'' = H) and (II, R = R' = R'' = H) by synthesis<sup>4,5</sup> of their respective dimethyl ethers (II, R = OCH<sub>3</sub>, R' = R'' = CH<sub>3</sub>) and (II, R = H, R' = R'' = CH<sub>3</sub>).

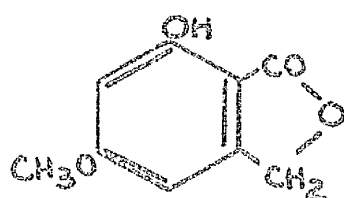


(I)

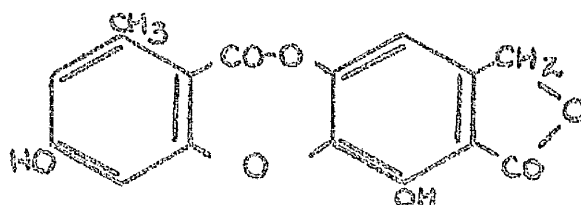


(II)

Vrköc, Herout and Sörm isolated a phenolic phthalide from Helichrysum Arenarium to which they have since assigned<sup>6</sup> the structure, 7-hydroxy-5-methoxyphthalide (III), that of a compound previously synthesised by Allison and Newbold.<sup>7</sup>

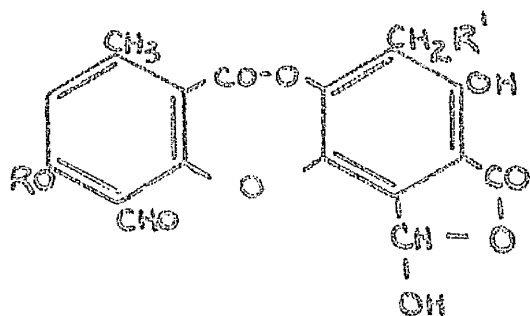


(III)

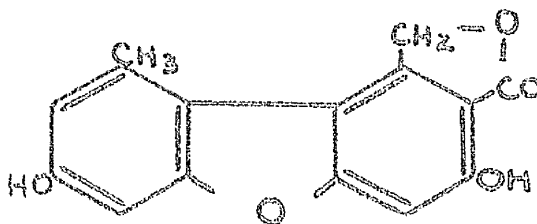


(IV)

Variolaric acid (IV) has been isolated from the lichen Lecanora parella,<sup>8</sup> while salazinic acid (V, R = H, R' = OH) occurs widely in the Parmelia family.<sup>9</sup> Stictic acid (V, R = CH<sub>3</sub>, R' = H) and norstictic acid (V, R = R' = H) have been found in Lobaria lichens<sup>10</sup> and strepsilin (VI) in Cladonia strepsilis Wain.<sup>11</sup> Products obtained by alkaline hydrolysis of some lichen depsidones have also been formulated as phthalide derivatives.<sup>12</sup>



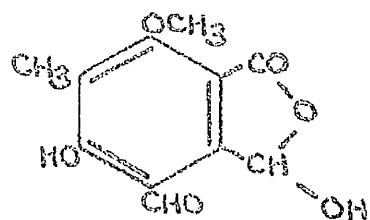
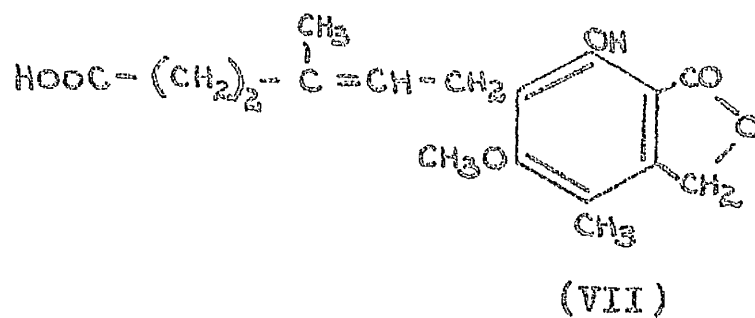
(V)



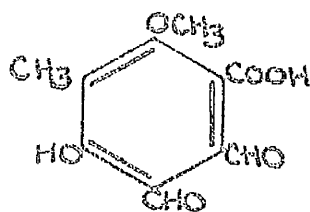
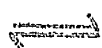
(VI)

From moulds of the Penicillium species a number of phthalide metabolic products have been isolated. Certain of these compounds have antibacterial and antifungal

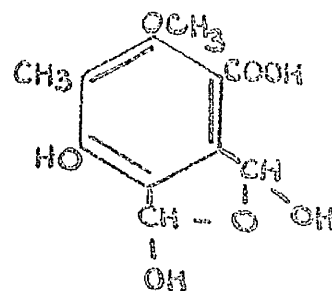
properties. From *P. brevi-compactum* was obtained myco-phenolic acid<sup>13</sup> (VII), while the hydroxyphthalides, cyclopaldic acid (VIII) and cyclopolic acid (IX) were isolated from *P. cyclopium* Westling<sup>14</sup> and *P. viridicatum*.<sup>15</sup> *P. gladioli* Machacek yielded gladiolic acid (X)<sup>16</sup> and dihydrogladiolic acid (XI),<sup>17</sup> having structures closely akin to (VIII) and (IX) respectively.



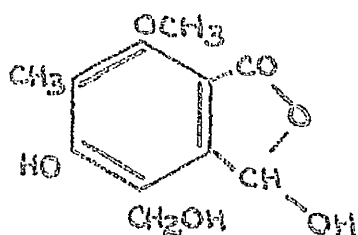
(VIIIa)



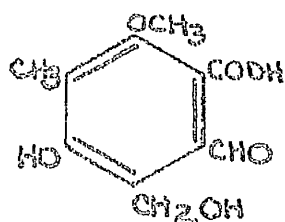
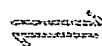
(VIIIb)



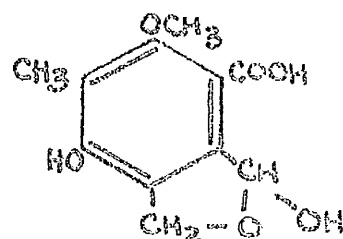
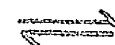
(VIIIc)



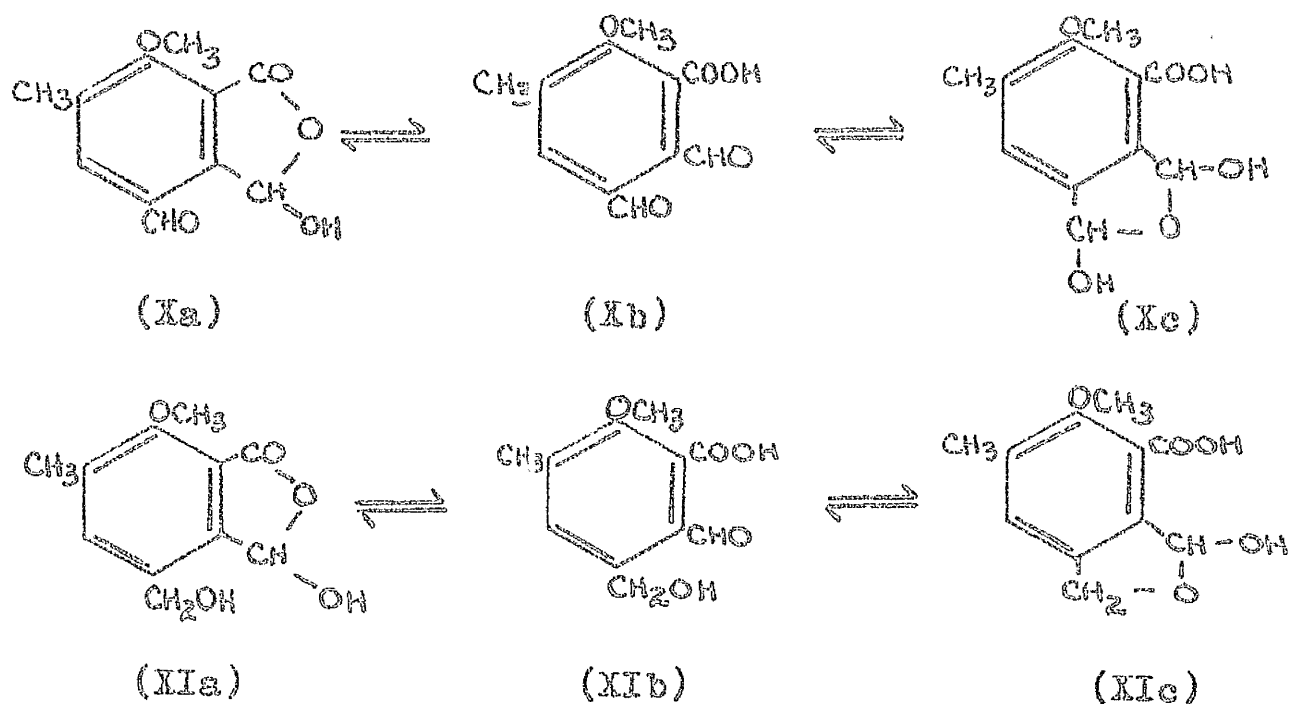
(IXa)



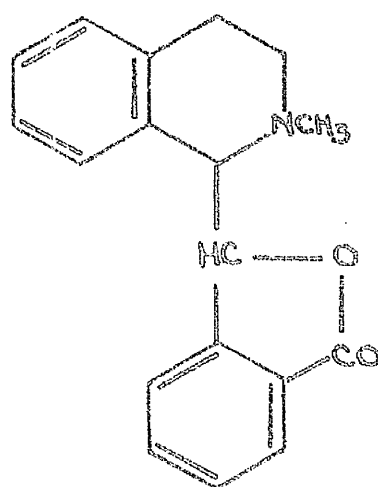
(IXb)



(IXc)



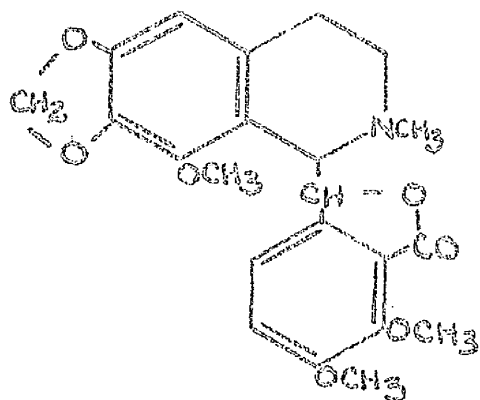
A group of eleven alkaloids, the phthalide-isoquinolines,<sup>18</sup> have been isolated from plants of the Papaveraceae and Berberidaceae families. All are derived by simple substitution of the basic structure (XII).



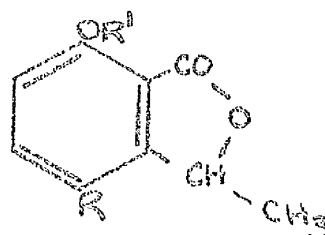
(XII)

Certain of these compounds yield simpler phthalides on degradation. For example, meconin (I) was obtained from narcotine (XIII) on heating with zinc and mineral acid.

Phthalides have been obtained as degradation products of other naturally occurring compounds also. For example, 7-hydroxy-3-methylphthalide (XIV,  $R = R' = H$ )<sup>19</sup> has been isolated from the alkaline degradation of terramycin and 4-chloro-7-methoxy-3-methylphthalide (XIV,  $R = Cl$ ,  $R' = CH_3$ ) from decarboxylation of a simple aureomycin derivative.<sup>20</sup>



(XIII)



(XIV)

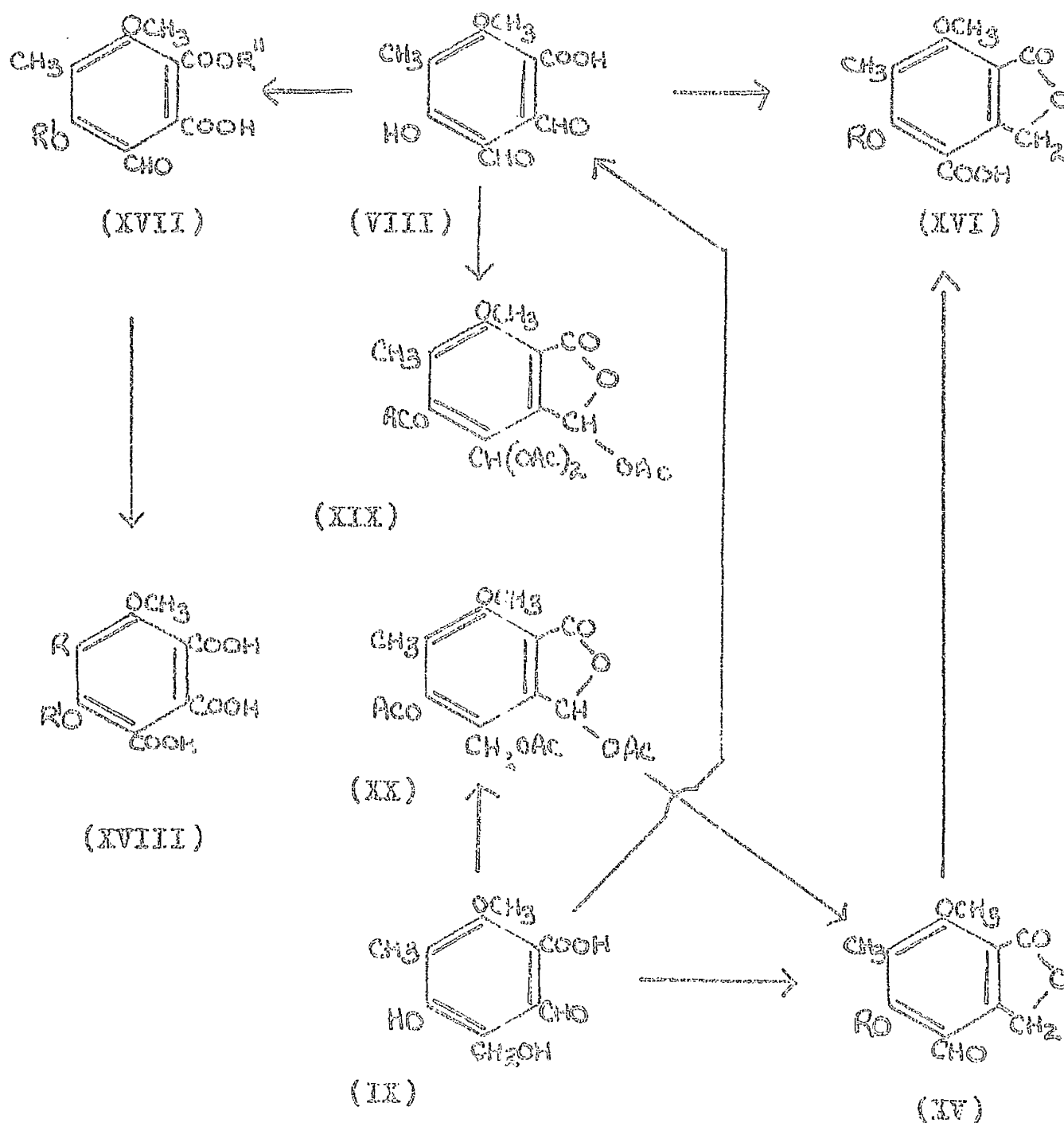
#### Chemistry of Cyclopaldic Acid and Cyclopolic Acid

The structures of cyclopaldic acid (VIII) and cyclopolic acid (IX) have been elucidated as a result of intensive degradative work by Raistrick *et al.*<sup>14</sup> and also, in the case of (IX), by infrared spectroscopic examination by Duncanson,

Grove and Zealley.<sup>21</sup> Both acids have been shown to exist in the form of keto-lactol tautomers as indicated above. Keto-lactol tautomerism in general, and in the case of cyclopaldic and cyclopolic acid will be discussed later. However in this section, for simplicity, structures (VIIIb) and (IXb) will be used when referring in general to cyclopaldic acid and cyclopolic acid as (VIII) and (IX) respectively.

Cyclopolic acid (IX) was readily oxidised to cyclopaldic acid (VIII) by potassium periodate and dilute sulphuric acid. By heating (IX) above its melting point in vacuo or by treating with dilute mineral acid there was obtained a white material which was named "cyclopolide" by the above authors.<sup>14</sup> By analogy with the compound formed on similar treatment of dihydrogladiolic acid (XI) Grove and coworkers<sup>21</sup> suggested formulation as (XV, R = H). The mechanism involved in the reaction will be discussed in conjunction with the chemistry of dihydrogladiolic acid.

Cyclopolide monomethyl ether (XV, R = CH<sub>3</sub>) when treated with cold alkaline potassium permanganate was converted to isocyclopaldic acid monomethyl ether (XVI, R = CH<sub>3</sub>). Isocyclopaldic acid (XVI, R = H) was prepared directly from cyclopaldic acid (VIII) by the treatment of the latter compound with boiling 2N. sodium hydroxide.



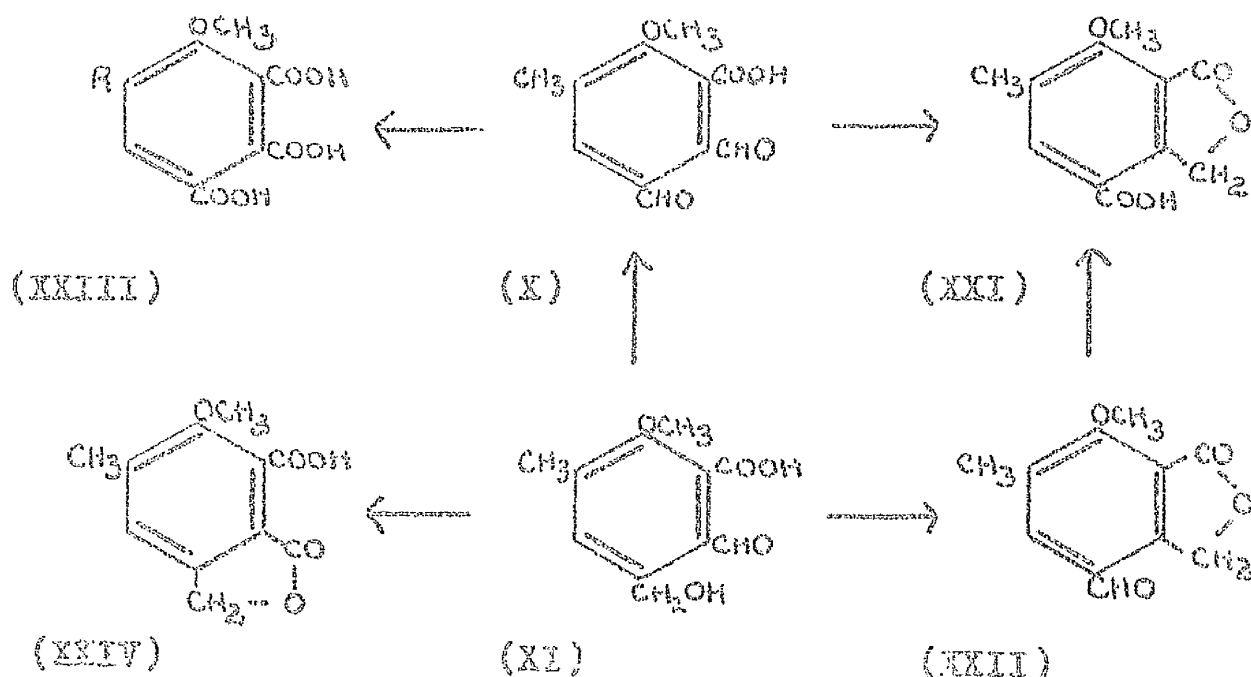
By oxidation of cyclopaldic acid at room temperature with alkaline hydrogen peroxide, oxycyclopaldic acid (XVII,  $\text{R}' = \text{R}'' = \text{H}$ ) was isolated, the methyl ester monomethyl ether

of which (XVII,  $R' = R'' = \text{CH}_3$ ) on further treatment with hot alkaline potassium permanganate produced a tetracarboxylic acid (XVIII,  $R = \text{COOH}$ ,  $R' = \text{CH}_3$ ) and with cold, a tricarboxylic acid (XVIII,  $R = R' = \text{CH}_3$ ).

Acetylation of cyclopaldic acid (VIII) furnished a tetra-acetate (XIX) while by similar treatment of cyclopolic acid (IX) a triacetate (XX) was formed, which on treatment with mineral acid yielded cyclopolide (XV,  $R = \text{H}$ ).

#### Chemistry of Gladiolic Acid and Dihydrogladiolic Acid

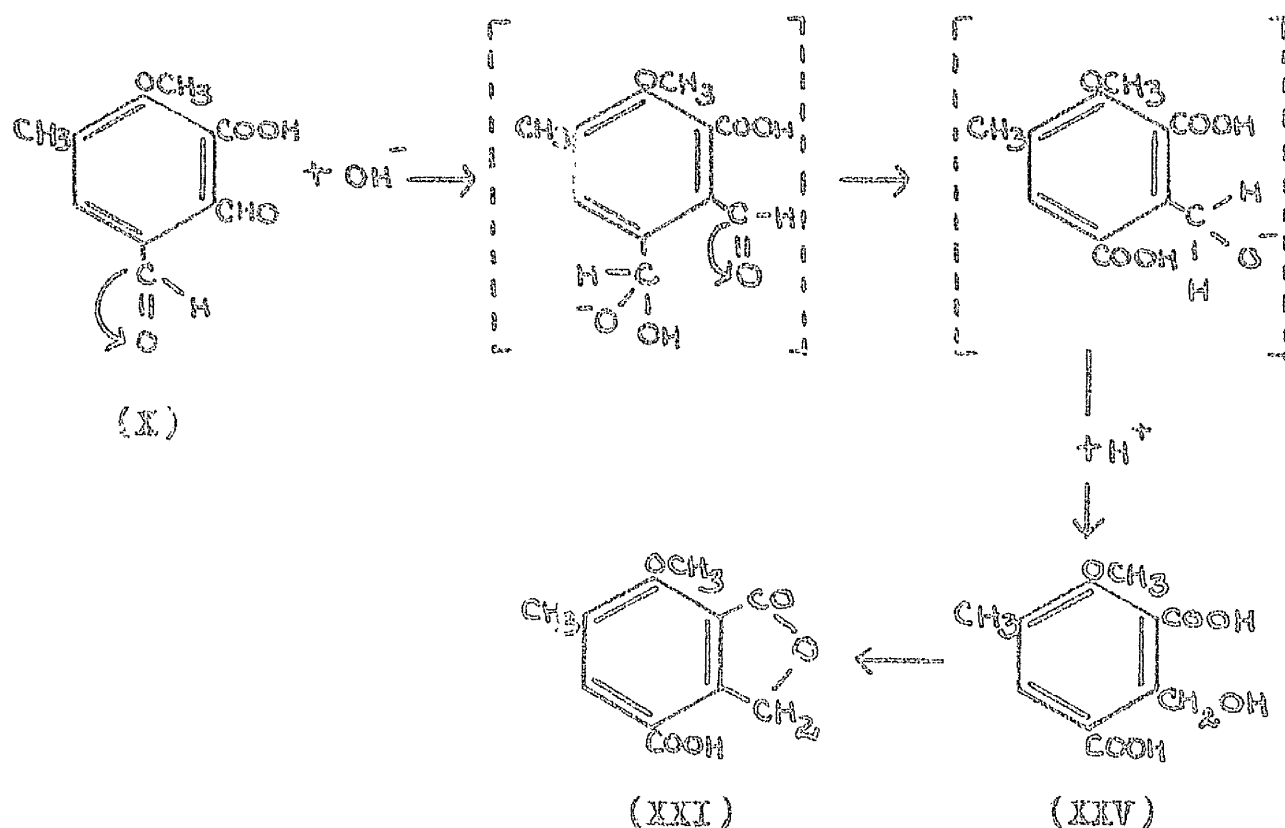
Similar work has been carried out by Raistrick and Ross<sup>17</sup> and by Grove and coworkers<sup>21,22</sup> on gladiolic acid (X) and dihydrogladiolic acid (XI) which, as might be expected from their close structural similarity to cyclopaldic acid (VIII) and cyclopolic acid (IX), undergo





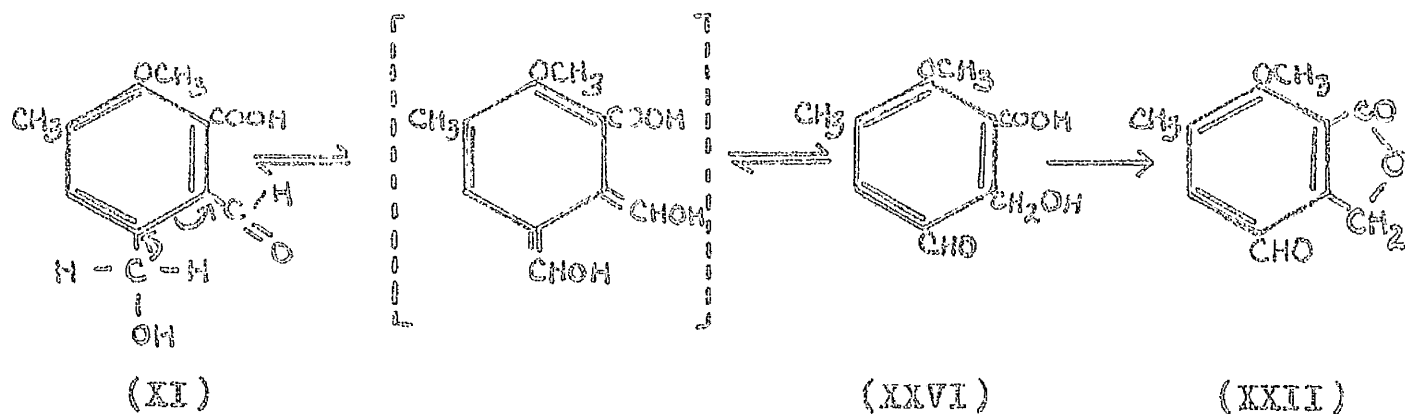
reactions very similar to those undergone by the latter compounds. Structures (Xb) and (XIb) will be used in the general discussion of gladiolic acid and dihydrogladiolic acid respectively.

Oxidation by potassium periodate and dilute sulphuric acid readily converted dihydrogladiolic acid (XI) to gladiolic acid (X), which on treatment with boiling 2N. sodium hydroxide produced isogladiolic acid (XXI). The reasons for the formation of a single product, (XXI), by this latter reaction have been discussed by Grove.<sup>22</sup> The mechanism was assumed by this author to involve the initial attack of a hydroxyl ion on (X) as shown. By this route



only one substituted hydroxymethylbenzoic acid is formed, (XXV). Lactonisation takes place completely in one direction because of steric hindrance caused by a methoxyl group in the ortho position to one of the carboxyl groups. Ring formation involving this carboxyl group has been shown to remove the steric strain.

Deoxygladiolic acid (XXII) was obtained from dihydrogladiolic acid (XI) by heating the latter compound in vacuo above its melting point, or by the action of dilute mineral acid. Duncanson, Grove and Zealley<sup>22</sup> have tentatively explained the formation of (XXII) from (XI) and that of cyclopolide (XV, R = H) from cyclopolic acid (IX) by postulation of a mechanism which, considering the case of dihydrogladiolic acid, involves the prototropic rearrangement of (XI) to produce the hypothetical intermediate (XXVI). The latter structure under conditions favouring the formation of a stable phthalide ring gives (XXII).



Dihydrogladiolic acid (XI) has been found to be oxidised in alkaline solution to 6-methoxy-5-methylphthalide-7-carboxylic acid (XXIV) by all mild oxidising agents. The structural significance of this reaction will be considered later. Like cyclopaldic acid, gladiolic acid (X) was shown to react with hot alkaline potassium permanganate to yield a tetracarboxylic acid (XXIII, R = COOH) and with cold to yield a tricarboxylic acid (XXIII, R = CH<sub>3</sub>).

### Keto-Lactol Tautomerism

In general there are numerous examples of this phenomenon, mainly  $\gamma$ -aldehydo- and  $\gamma$ -keto acids, which may be represented by the partial structures (XXVII) and (XXVIII).



Two types of esters may be obtained. The normal ester, as for example in the partial structure (XXVII, R = CH<sub>3</sub>, R' = H), is formed by the action of an alkyl halide on the silver salt of the corresponding acid (XXVII,

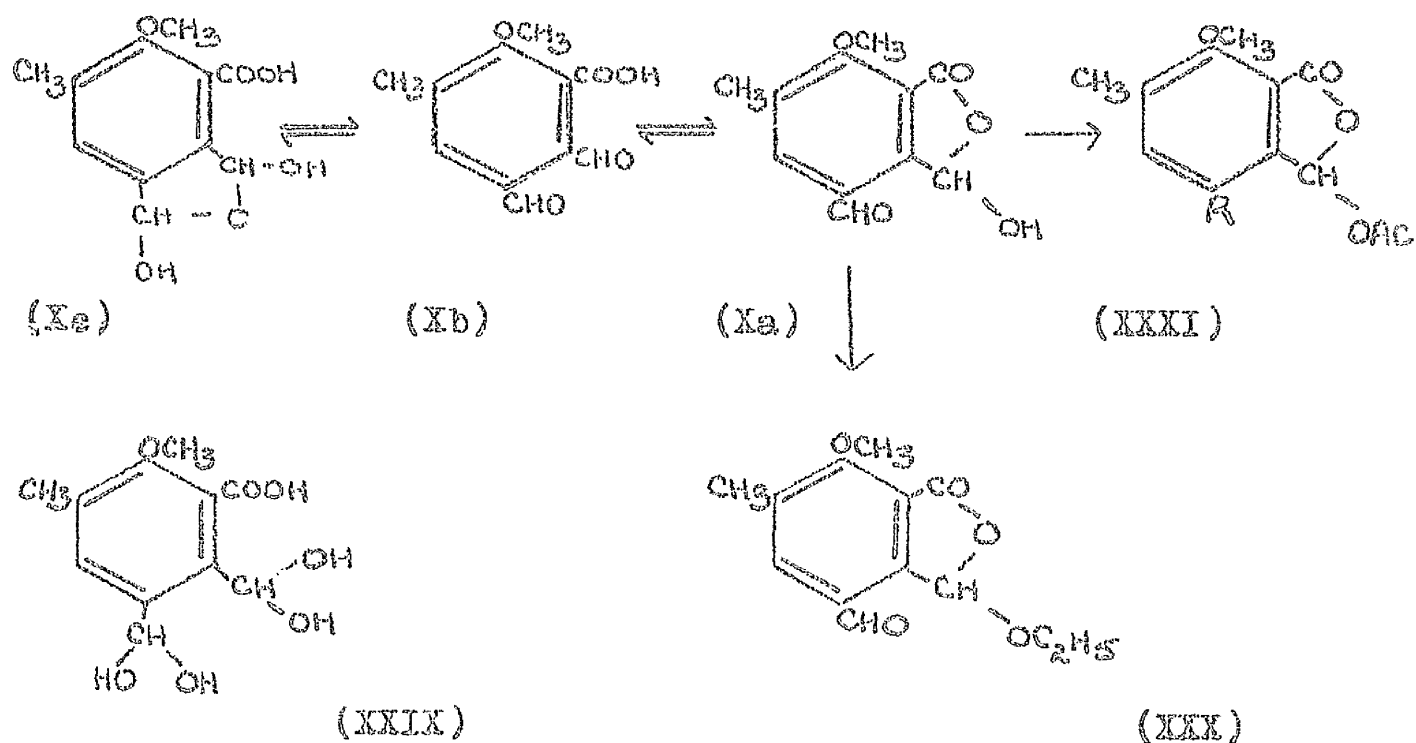
$R = R' = H$ ), whereas the direct reaction of the acid with an alcohol in the presence of catalyst produces the pseudo ester as in (XXVIII,  $R = CH_3$ ,  $R' = H$ ). The normal esters retain the characteristic aldehyde or ketone group reactions which may be used to identify them, while the pseudo esters are completely devoid of such properties.

Grove and Willis,<sup>23</sup> by use of infrared spectroscopy, obtained some general data by use of which the lactol and open chain forms of tautomers could be readily distinguished by examination of the frequencies of the absorption bands due to the  $C = O$  groups.

Gladiolic acid (X) has been shown by Grove<sup>24</sup> by infrared measurements to exist largely as the lactol (Xa) in the solid state. A band was found at  $1735\text{ cm.}^{-1}$  corresponding to that of a hydrogen-bonded phthalide, the hindrance being due to intermolecular bonding with hydroxyl groups in the 3-position. Absorption bands at  $3225\text{ cm.}^{-1}$  and  $1700\text{ cm.}^{-1}$  assignable to a hindered hydroxyl group and an aromatic aldehyde group respectively were also observed.

Moreover, the same worker<sup>24,25</sup> has further shown from U.V. studies that equilibrium in solution depends on pH. In aqueous and non-polar solutions the lactol was found to predominate, while in alkali the gladiolic anion was shown, by comparison with model compounds, to have either the

dihydroxyphthalan structure (Xc) or the bis(dihydroxy-methyl) structure (XXIX). (Xc) was considered to be the more probable structure since the hydration phenomenon was observed only in the gladiolic anion. No previous spectroscopic evidence has been found showing hydration in aqueous solution as having taken place where only one free formyl group was present, as would be required if (XXIX) were the correct structure of the tautomer.

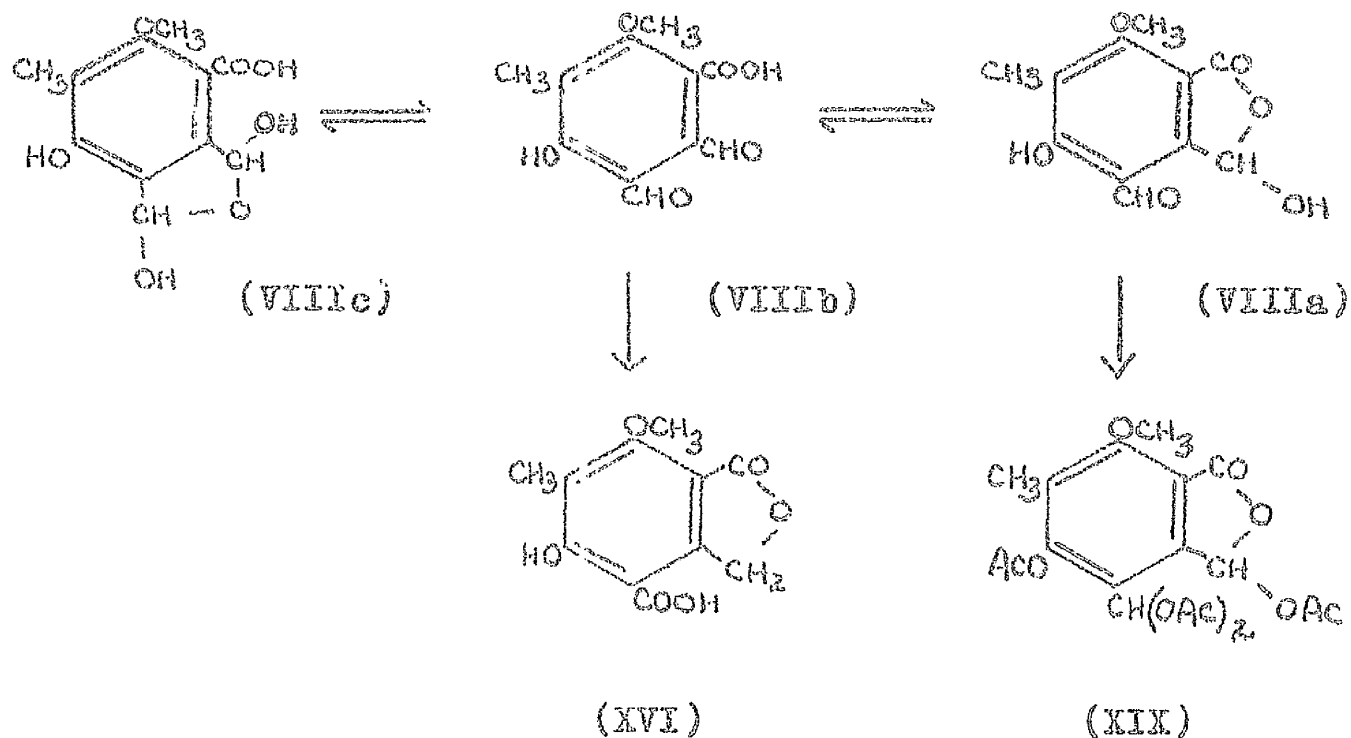


Pseudo esters have been prepared<sup>22, 24</sup> from gladiolic acid by treatment with an alcohol in the presence of an acid catalyst. Formation of the pseudo ester, for example

ethyl gladiolate (XXX), was indicated by the absorption in the infrared region at  $1770\text{ cm.}^{-1}$  due to the phthalide carbonyl and at  $1705\text{ cm.}^{-1}$  due to the formyl group.

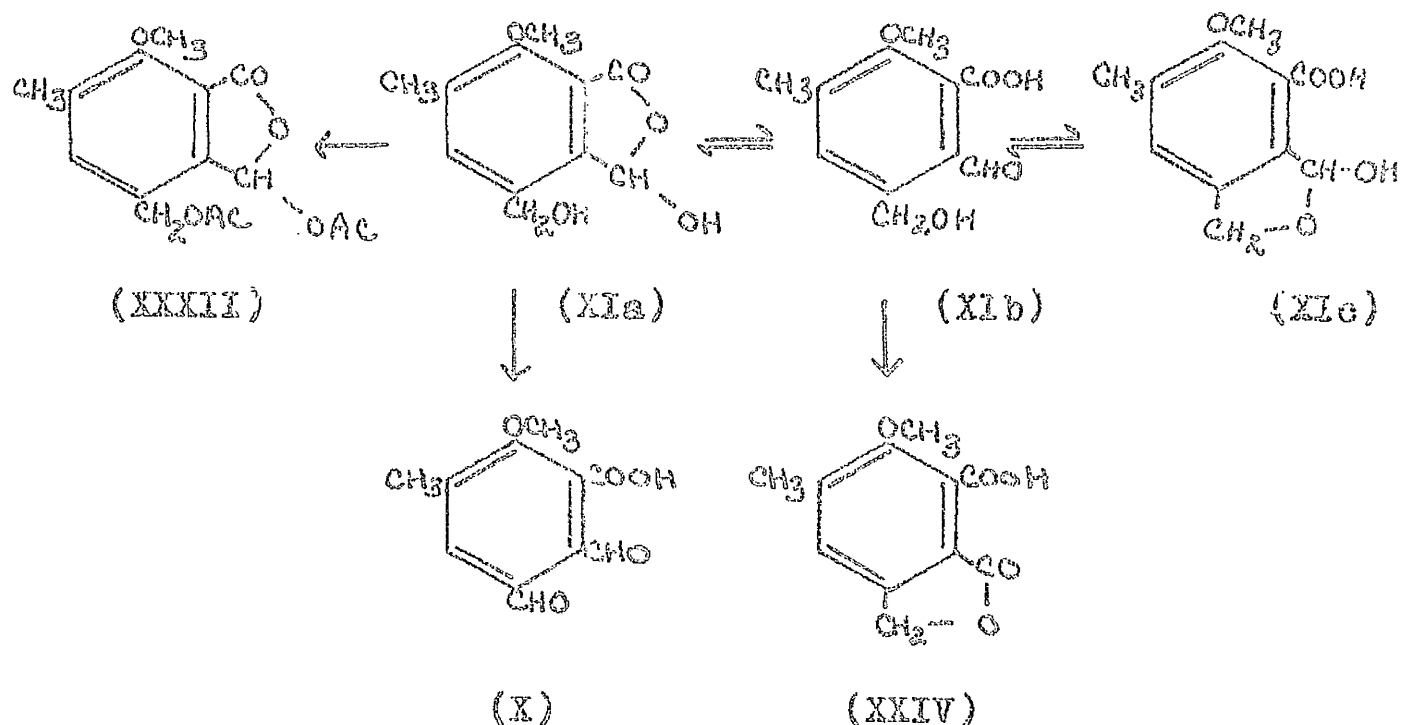
Acetylation of (X) yielded under varying conditions neutral derivatives formulated as (XXXI,  $R = \text{CHO}$ ) and (XXXI,  $R = \text{CH}(\text{OAc})_2$ ). The infrared absorption band occurring at  $3225\text{ cm.}^{-1}$  due to the 3-hydroxyl group in the lactol, disappeared in the monoacetate while the phthalide group, freed of interference due to intermolecular hydrogen-bonding with the lactol groups of neighbouring molecules, absorbed at  $1768\text{ cm.}^{-1}$  (thereby masking the absorption due to the acetyl band introduced). The band at  $1700\text{ cm.}^{-1}$  remained unchanged in the monoacetate. In the triacetate, however, the latter band disappeared and was substituted by one at  $1785\text{ cm.}^{-1}$  due to the  $-\text{CH}(\text{OAc})_2$  group.

Cyclopaldic acid must react as the lactol (VIIIa) in the formation of (XIX) by acetylation, while (XVI) is clearly formed by the reaction of the acid as the open chain tautomer (VIIIb). No infrared nor ultraviolet data for cyclopaldic acid have been reported, and the existence of any third structural form (VIIIc), analogous to (Xc), has not been substantiated, although there seems no reason why it should not exist.



Cyclopolic acid (IX) and dihydrogladiolic acid (XI) have also been shown<sup>21</sup> to exist in tautomeric forms. The lactol forms predominate in the solid phase and in acid solution, while in alkali the ions exist largely in the open chain form.

Evidence corroborating the assignment of the structural forms of dihydrogladiolic acid (XI) as shown, was obtained<sup>21</sup> from examination of the ultraviolet spectrum of the acid in aqueous and in alkaline solution. Spectra close to those for the lactol and open chain forms of gladiolic acid were obtained. However, in alkaline solution the typical



absorption of the conjugated benzenoid and carbonyl chromophores was found to be absent. This was ascribed either to steric factors or to hydration of the formyl group by intramolecular reaction, which would yield (XIc) as a third possible molecular species of dihydrogladiolic acid.

Acetylation of dihydrogladiolic acid (XI) yielded a diacetate to which the structure (XXXII) has been assigned<sup>21</sup> from infrared data. This reaction confirmed that dihydrogladiolic acid reacts under certain conditions in the lactol form (XIa).

The equilibrium state between (XIa) and (XIb) accounts

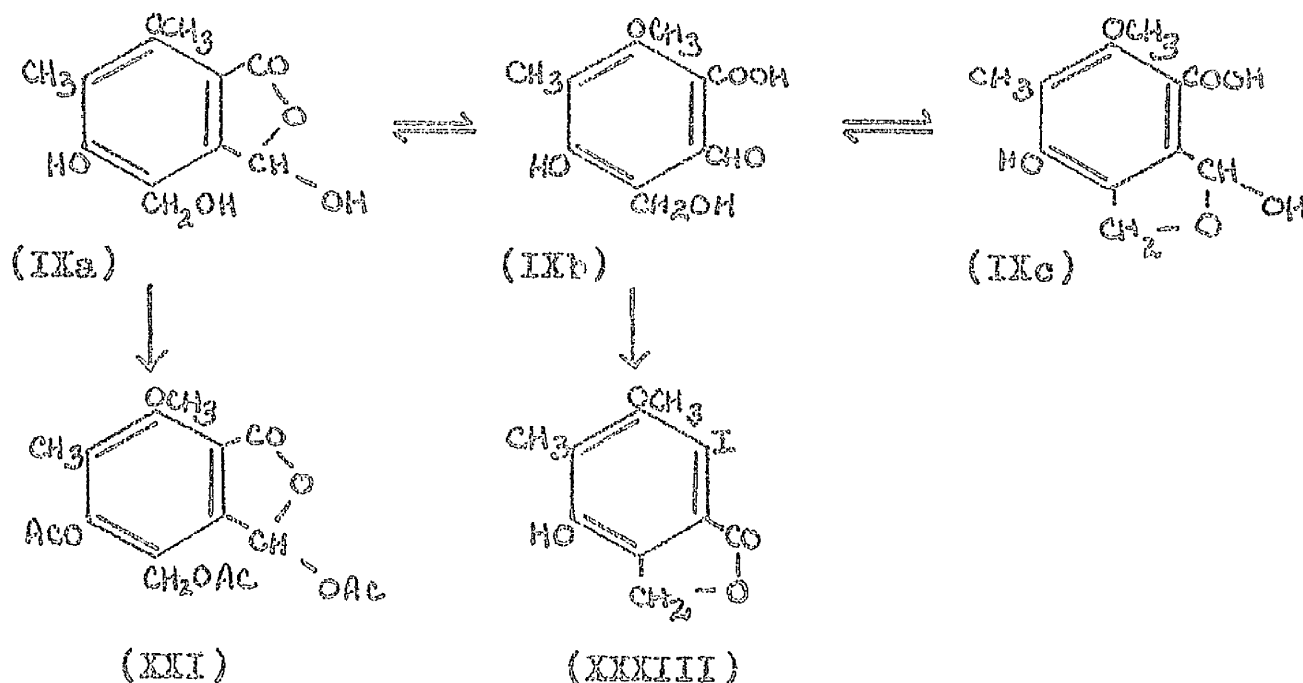


for the differences in the products obtained by mild acid and mild alkaline oxidation of dihydrogladiolic acid. In acid the hydroxymethyl group is the more sensitive grouping and gladiolic acid (X) results via the lactol forms (XIa) and (Xa). In alkali, however, the open chain form (XIb) allows preferential attack on the formyl group and 6-methoxy-5-methylphthalide-7-carboxylic acid (XXIV) is produced.

Cyclopolic acid in the solid state was found<sup>21</sup> to absorb in the infrared region at  $1768\text{ cm.}^{-1}$ . This fact implied that no carboxyl group was present and that the compound, when solid, existed largely in the lactol form (IXa), a fact which was confirmed by the formation of a triacetate (XX) on acetylation.

In an analogous manner to the oxidation of (XI) with mild alkaline oxidising agents, as for example with alkaline iodine, cyclopolic acid was oxidised by the same reagent to finally yield 4-hydroxy-7-iodo-6-methoxy-5-methylphthalide (XXXIII). The replacement of the carboxyl group at the 7-position by iodine in this case must presumably be attributable to the activation of the ring at that point by the hydroxyl group in the para position to it. No evidence has been reported to substantiate the existence

of a third structural form of cyclopolic acid (IXc), stable in alkali and analogous to (XIc).

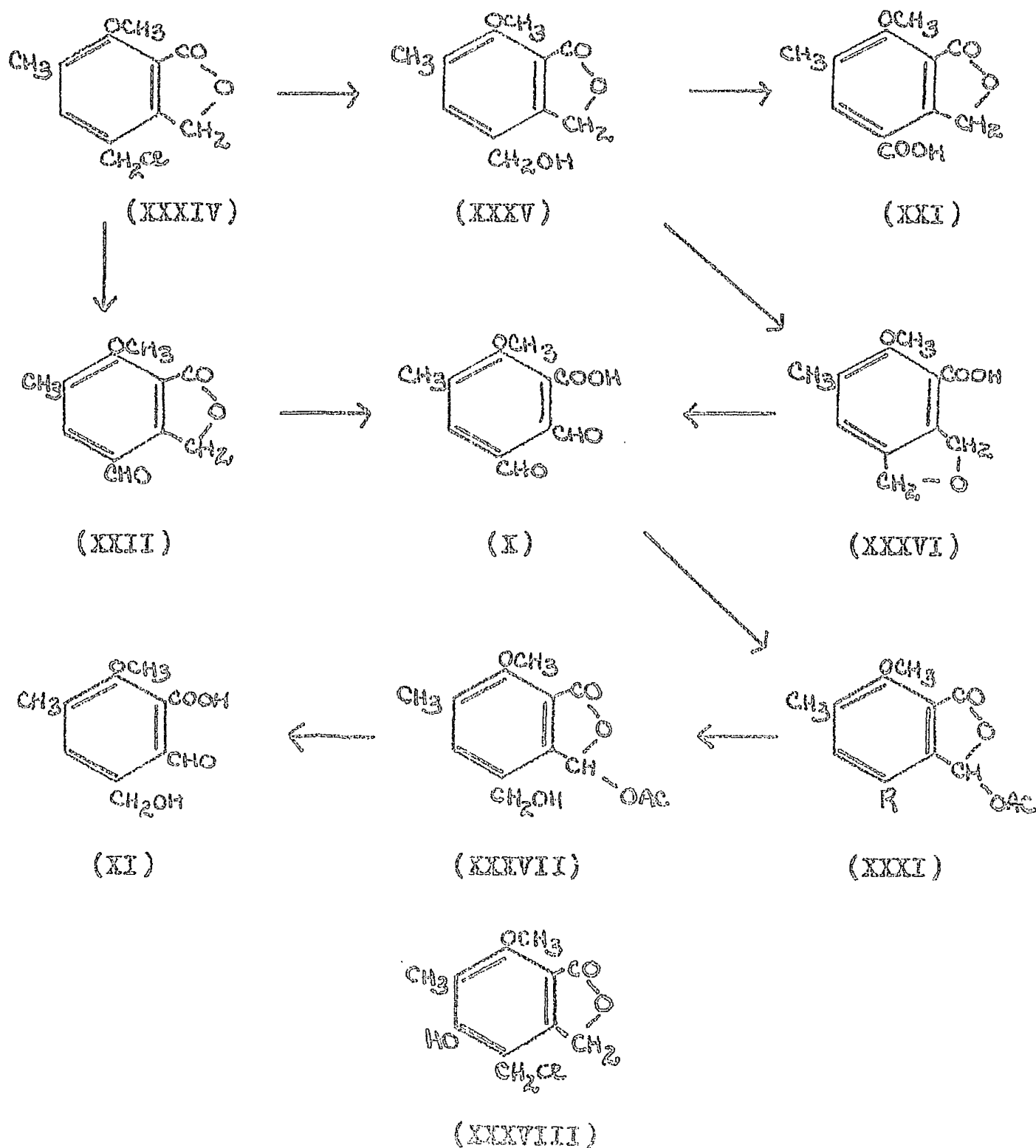


#### Total Syntheses of Gladiolic Acid and Related Compounds

Total syntheses have been reported for gladiolic acid (X), dihydrogladiolic acid (XI), deoxygladiolic acid (XXII), and isogladiolic acid (XXI) the latter parts of which involve reactions which interrelate the four compounds and which could possibly be of considerable value in the projected syntheses of cyclopaldic acid (VIII) and cyclopolic acid (IX).

The key compound in the synthetic route to all four is 4-chloromethyl-7-methoxy-6-methylphthalide (XXXIV). This material may be synthesised by the route devised by Brown

and Newbold,<sup>26</sup> a route not suitable, however, for the synthesis of the analogous key compound in the cyclopaldic acid and cyclopolic acid series, 4-chloromethyl-5-hydroxy-7-methoxy-6-methylphthalide (XXXVIII).



The synthetic route to gladiolic acid (X) reported<sup>27,28</sup> involved the treatment of (XXXIV) with three mols. of N-bromo-succinimide followed by hydrolysis with water to yield deoxygladiolic acid (XXII), which was oxidised by potassium periodate to yield gladiolic acid (X).

A number of years later Blair, Logan and Newbold<sup>29</sup> reported a synthesis by a somewhat different route. (XXXIV) was hydrolysed to 4-hydroxymethyl-7-methoxy-6-methylphthalide (XXXV) by heating with sodium carbonate. Rearrangement of (XXXV) was brought about by sodium methoxide in methanol to yield 5-methoxy-6-methylphthalan-4-carboxylic acid (XXXVI), which was converted to gladiolic acid (X) by treatment with two mols. of N-bromo-succinimide followed by water.

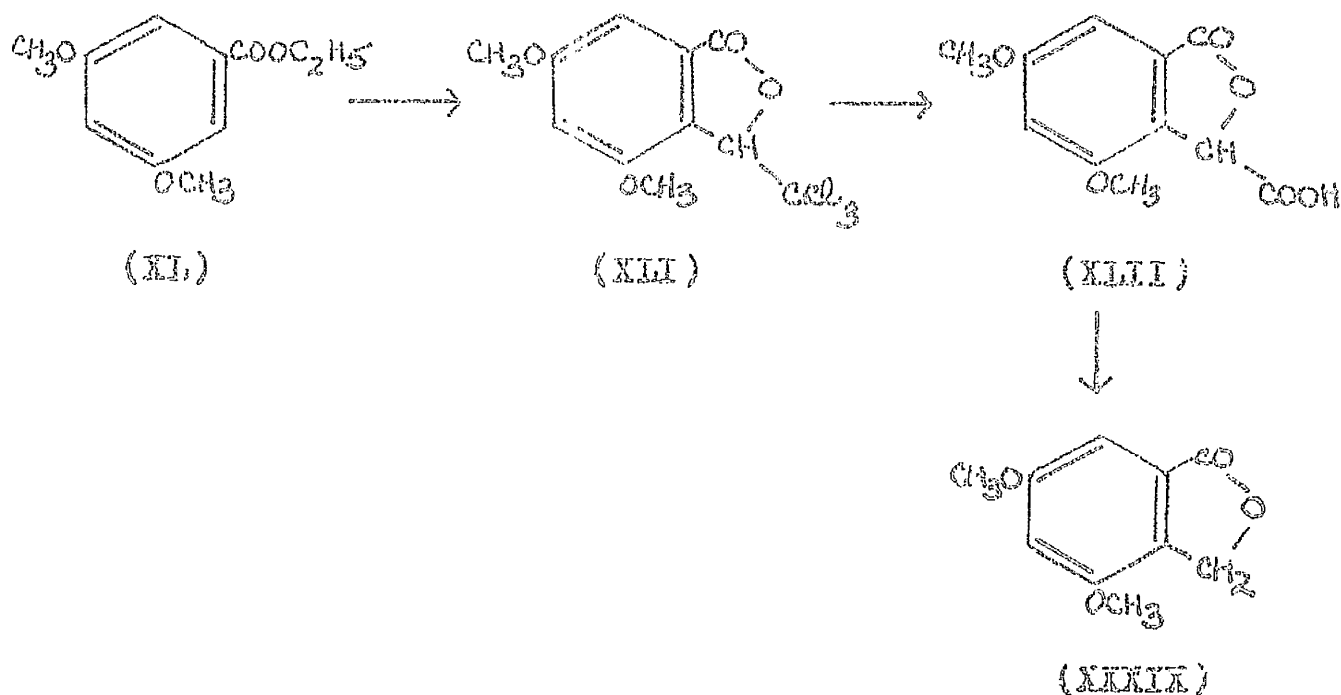
A synthetic route to dihydrogladiolic acid (XI) from gladiolic acid (X) was developed by Duncanson, Grove and Zealley.<sup>21</sup> The monoacetate of gladiolic acid (XXXI, R = CHO) on platinum catalysed hydrogenation yielded dihydrogladiolic acid monoacetate (XXXVII) from which (XI) was readily obtained by alkaline hydrolysis.

Isogladiolic acid (XII) was formed by oxidation of 4-hydroxymethyl-7-methoxy-6-methylphthalide (XXXV) by potassium permanganate in acid solution.<sup>26</sup>

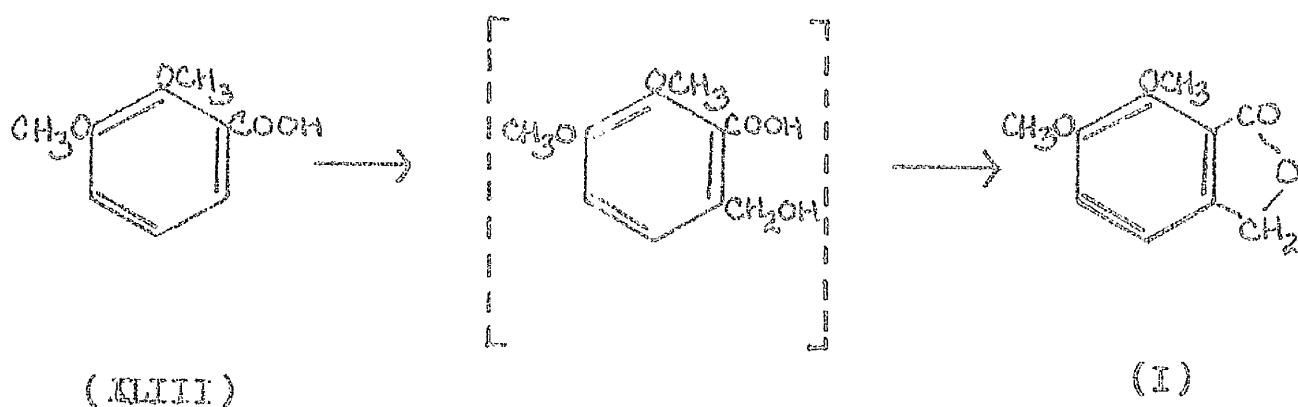
## General Methods of Phthalide Synthesis

Few general methods have been evolved for the preparation of phthalides, although many syntheses of specific phthalide compounds have been reported. These have been reviewed in detail by Elderfield.<sup>30</sup>

A method of obtaining a fairly wide range of ring-substituted phthalides was put forward by Fritsch.<sup>1</sup> By this route 4,6-dimethoxyphthalide (XXXIX), for example, could be synthesised from ethyl 3,5-dimethoxybenzoate (XI) by condensation of the latter compound with chloral in 90% sulphuric acid to give (XII), which on alkaline hydrolysis yielded (XIII). Decarboxylation of (XIII) at 180°C yielded (XXXIX).

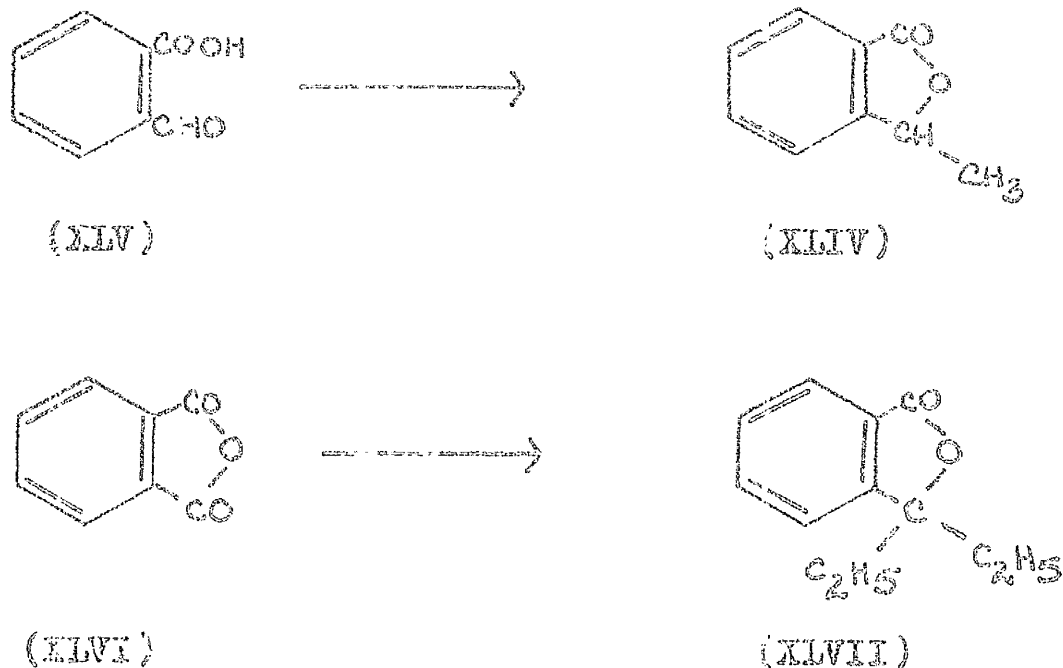


A shorter route was that of Edwards, Perkin and Stoyle,<sup>31</sup> an example of which is the condensation of ortho-veratric acid (XLIII) with formaldehyde in concentrated hydrochloric acid to give neconin (I). The method, however, is not completely general and its scope and limitations have been investigated by Charlesworth and his co-workers.<sup>32</sup>



Phthalides substituted in the hetero ring have also been prepared. One of the most general methods of formation of a mono-substituted derivative involves the treatment of the corresponding phthalaldehydic acid with Grignard reagent. 3-Methylphthalide (XLIV) was prepared from phthalaldehydic acid (XLV) by the action of methyl magnesium bromide.<sup>33,34</sup> Disubstituted phthalides have been prepared<sup>35</sup> by the reaction of a controlled amount of the corresponding Grignard reagent on phthalic anhydride (XLVI) as indicated in the synthesis of 3,3-diethylphthalide

(XLVII) using ethyl magnesium bromide.

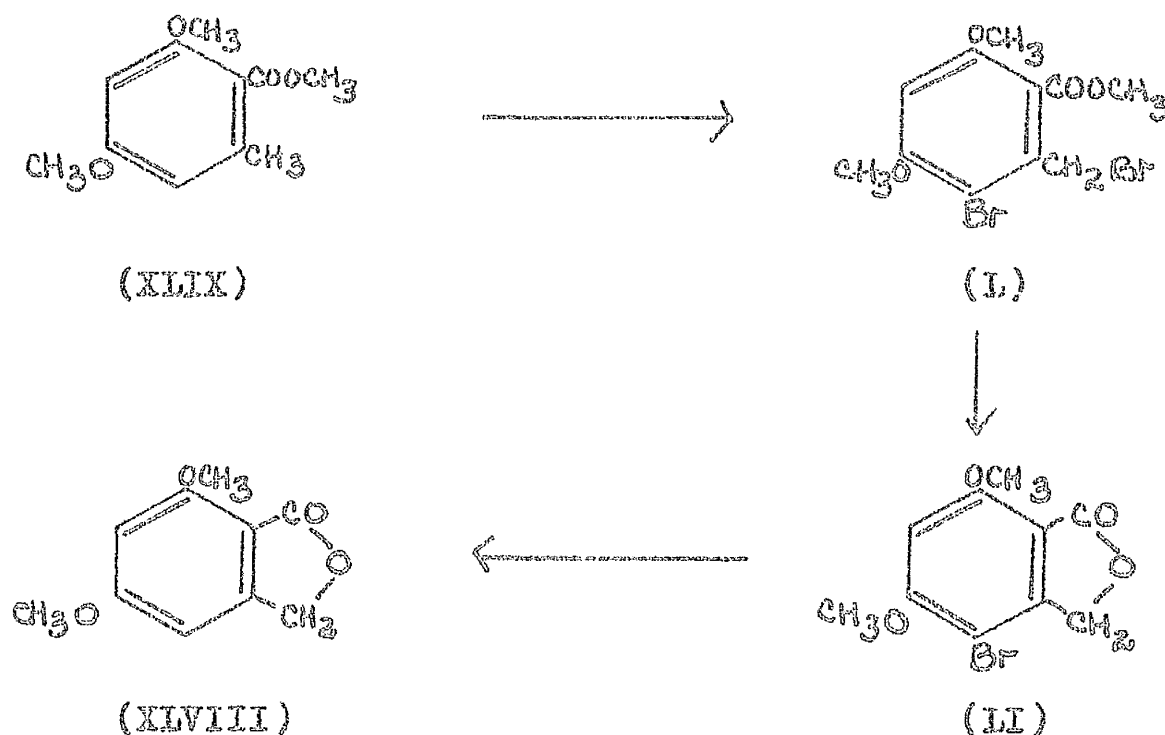


Perhaps the most general method so far described for the synthesis of substituted phthalides employs the photo-bromination technique developed by Eliel *et al.*<sup>36,37</sup> for the addition of bromine to the methyl side chain in substituted toluenes. In this, the compound to be brominated, dissolved in carbon tetrachloride, was treated dropwise with a calculated molar equivalent of bromine in carbon tetrachloride, whilst the solution was maintained at boiling point and irradiated by a suitably powerful incandescent lamp.

The method had been previously used in general syntheses<sup>38-46</sup> but yields, where reported, were poor. The conditions employed by these earlier workers, however, conformed to no standard. Sunlight,<sup>39,40,43</sup> a mercury arc lamp<sup>43,46</sup> and a tungsten lamp<sup>41,42,44,45</sup> have each been applied as the source of energy. One method recommended anhydrous conditions,<sup>41</sup> while in another<sup>46</sup> water was added to dissolve the hydrogen bromide formed in the reaction. Iodine, added as a catalyst in one case,<sup>40</sup> was found to inhibit the reaction in another.<sup>36</sup> The majority of the procedures used either carbon tetrachloride or carbon disulphide, although in a few cases a solvent was not employed.<sup>42,44</sup>

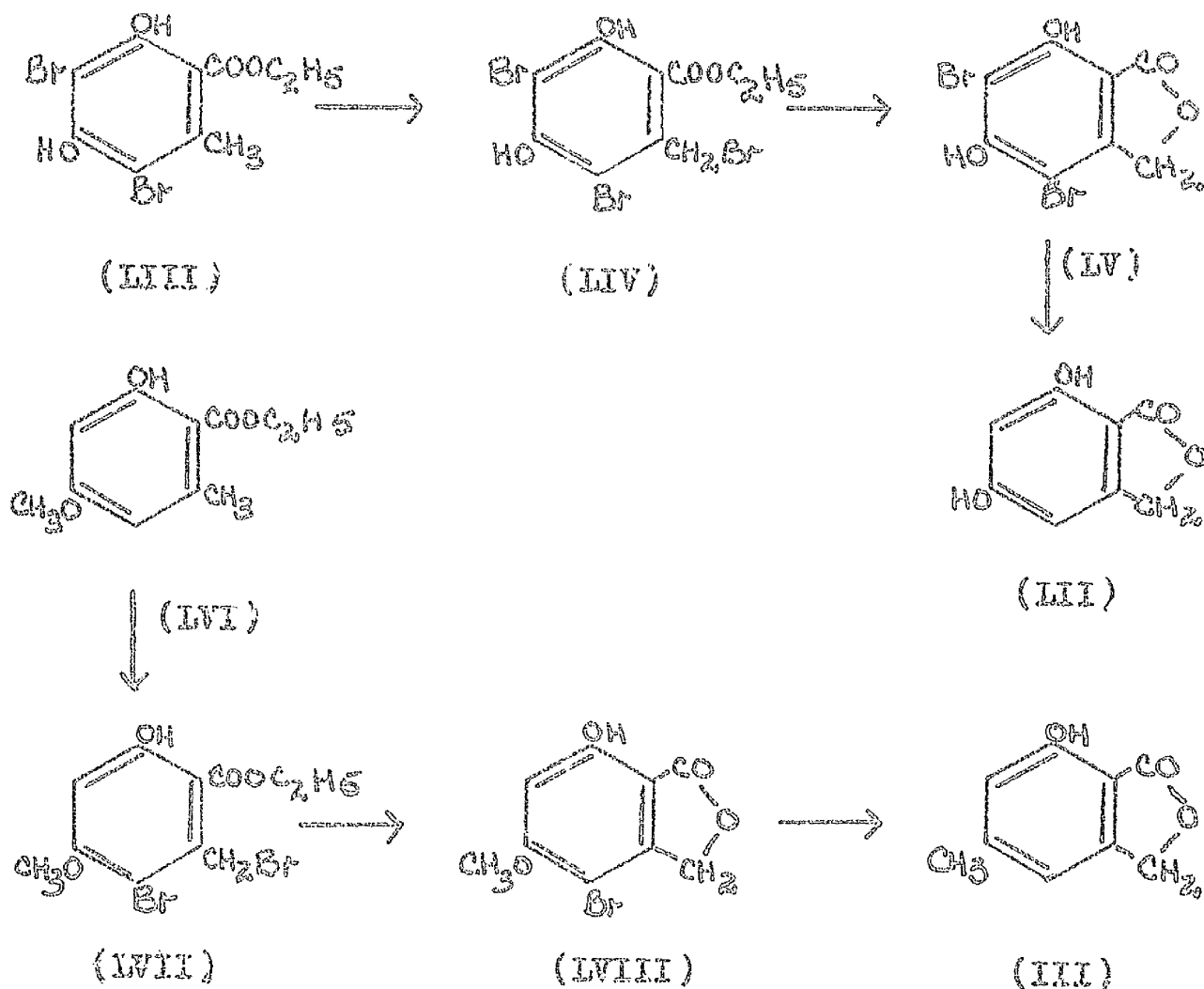
More recently Logan and Newbold<sup>47</sup> have used the method of Eliel to synthesise 5,7-dimethoxyphthalide (XLVIII) from methyl orsellinate dimethyl ether (XLIX). Treatment of (XLIX) with two mols. of bromine gave on irradiation by tungsten lamp methyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate (I) which, on alkaline hydrolysis, yielded 4-bromo-5,7-dimethoxyphthalide (II). 5,7-Dimethoxyphthalide (XLVIII) was obtained by hydrogenation of (II) using platinum catalyst in ethyl acetate.





Allison and Newbold<sup>7</sup> extended the procedure to the synthesis of 5,7-dihydroxyphthalide (LII) and 7-hydroxy-5-methoxyphthalide (III).

In the synthesis of (III), ethyl 3,5-dibromo-4,6-dihydroxy-2-methylbenzoate (LIII) was treated with 1 mol. of bromine in the manner previously outlined and ethyl 2-bromomethyl-3,5-dibromo-4,6-dihydroxybenzoate (LIV) was isolated, hydrolysis of which yielded 4,6-dibromo-5,7-dihydroxyphthalide (IV). This compound was in turn converted to 5,7-dihydroxyphthalide (LII) by hydrogenation using palladium on calcium carbonate as catalyst and aqueous sodium hydroxide as solvent.

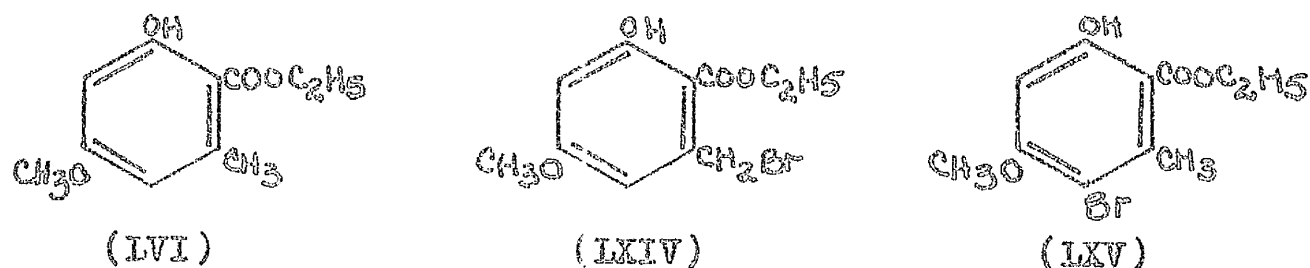
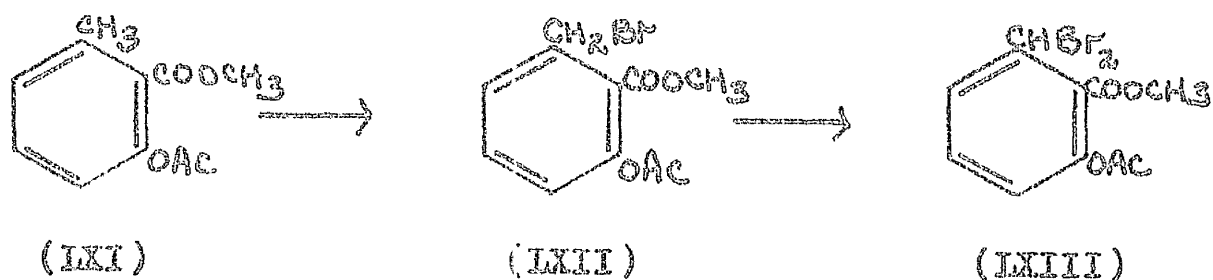
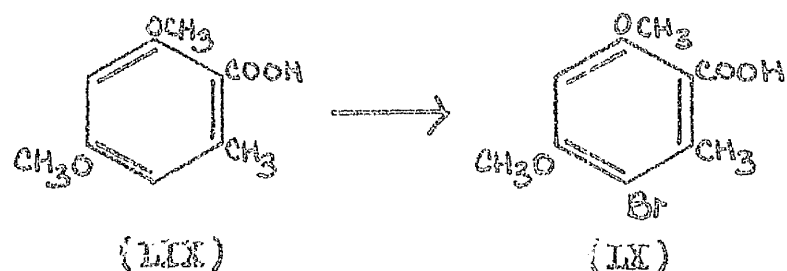


To obtain 7-hydroxy-5-methoxyphthalide (III), ethyl everninate (ethyl 6-hydroxy-4-methoxy-2-methylbenzoate) (LVI) was used as starting material. The latter compound, on treatment with two mols. of bromine, yielded ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (LVII), which on hydrolysis yielded 4-bromo-7-hydroxy-5-methoxyphthalide (LVIII). Hydrogenolysis of this material by palladium on calcium carbonate in alkali gave 7-hydroxy-5-methoxyphthalide (III).

Since the evidence available is somewhat contradictory, no definite rule can be postulated as to the positions at which bromine will most readily enter an aromatic molecule on photobromination. Logan and Newbold<sup>47</sup> found that photobromination of orsellinic acid dimethyl ether (LIX) with  $1\frac{1}{2}$  mols. of bromine yielded 3-bromo-4,6-dimethoxy-2-methylbenzoic acid (IX), while treatment of methyl orsellinate dimethyl ether (XLIX) with two mols. of bromine furnished methyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate (I). On the basis of these results the authors suggested that activation of the side chain methyl group by bromination of the adjacent nuclear position was necessary for its subsequent bromination.

On the other hand, Eliel et al.<sup>37</sup> found that methyl 2-acetoxy-6-methylbenzoate (LXI) yielded on addition of one mol. of bromine, methyl 2-acetoxy-6-bromomethylbenzoate (LXII), while addition of a further mol. gave methyl 2-acetoxy-6-dibromomethylbenzoate (LXIII).

Allison and Newbold<sup>7</sup> later showed that the point of addition of bromine was influenced by minor changes in the experimental conditions used. On photobromination of ethyl everninate (LVI) with one mol. of bromine under completely anhydrous conditions, ethyl 2-bromomethyl-6-



hydroxy-4-methoxybenzoate (LXIV) was the sole product, side chain bromination having taken place entirely. When a little methanol was present nuclear substitution took place to a large extent, the major product from the reaction being ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (LXV). Only a small amount [ $<10\%$ ] of ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (LXIV) was isolated.

As a result of the work of Allison and Newbold<sup>7</sup> the yields obtained by the photobromination route to phthalide derivatives have been improved by a novel method of hydrolysis of orthobromomethyl esters to the corresponding phthalides, carried out by refluxing the former compounds in aqueous dioxan. Alkaline hydrolysis of (LIV) and (LVII) using either aqueous sodium hydroxide or aqueous sodium carbonate, was found to proceed in very low yield with considerable discolouration. Hydrolysis by refluxing the materials in aqueous dioxan proceeded in 85-90% yield. The latter method was found to be even more advantageous since the product separated in a relatively high state of purity on concentration of the solvent, no discolouration or decomposition of the phenolic compounds having occurred. The reaction was also shown to proceed cleanly, although in lower yield, in a solution of aqueous methanol or aqueous ethanol.

Due to the liberation of hydrogen bromide the reaction took place under mildly acidic conditions. When the acid concentration was raised by the addition of small amounts of dilute hydrochloric acid to the hydrolysis reaction of ethyl 2-bromomethyl-3,5-dibromo-4,6-dihydroxybenzoate (LIV) with aqueous dioxan, the yield of phthalide dropped to 16%.

The photobromination and hydrolysis techniques just

described have been extensively employed in the present work.

### Infrared Spectra of Phenolic Phthalides

Further work by Allison and Newbold<sup>7</sup> extended the general data on the infrared spectra of hydroxyphthalides, accumulated by Duncanson, Grove and Zealley.<sup>48</sup>

The latter authors compared the carbonyl stretching frequencies of 7-hydroxyphthalides and 4-hydroxyphthalides in dilute solution and found that due to intramolecular hydrogen-bonding there was a characteristic lowering of the frequency of the former compounds. In the solid state the lowering of the frequencies in both cases was attributed to intermolecular hydrogen-bonding. In the same investigation it was also noted that the carbonyl frequencies of orthohydroxybenzoic acid esters were very much lower still, due to stronger intramolecular hydrogen-bonding.

Allison and Newbold<sup>7</sup> found a similar difference between the carbonyl frequencies of the 7-hydroxyphthalides and the 7-methoxyphthalides. All the 7-hydroxyphthalides investigated absorbed in the range 1732-1748  $\text{cm.}^{-1}$  while 7-methoxyphthalides absorbed in the range 1761-1764  $\text{cm.}^{-1}$ . They also compared the absorption frequencies of orthohydroxybenzoic acid esters and orthomethoxybenzoic acid esters. The former were found to absorb in the range 1655-1667

cm.<sup>-1</sup> and the latter in the range 1721-1724 cm.<sup>-1</sup>. These results confirmed that the lowering of the frequency of absorption of orthohydroxybenzoic acid esters due to hydrogen-bonding is markedly greater than that of the corresponding phthalides.

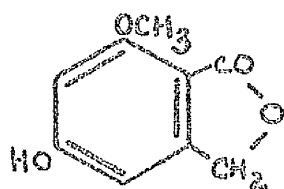
In the course of further work Duncanson, Grove and Zealley<sup>48</sup> observed from molecular models that, due to strain in the lactone ring of a phthalide, the carbonyl group is bent away from the 7-hydroxyl group to such an extent that the O-H-O distance approaches 3 Å, the limit for hydrogen-bond formation.<sup>50</sup> A bond of such a length would thus be expected to be weak. The strength of the hydrogen-bond in the case of the ester is due to its situation in an unstrained six-membered ring.

T H E O R E T I C A L

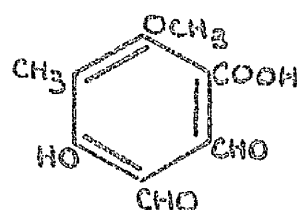


## General Objectives

In the work to be described, investigations have been carried out with a view to developing synthetic routes to 5-hydroxy-7-methoxyphthalide (LXVI) and cyclopaldic acid (VIII).

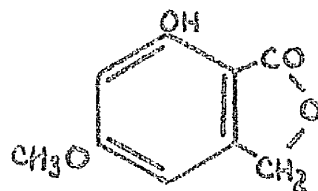


(LXVI)



(VIII)

The work on (LXVI) was initiated in order to confirm by synthetic means that the phthalide isolated from Helichrysum Arenarium was, in fact, 5-hydroxy-7-methoxyphthalide as suggested privately by Herout. The same author, however, at a later date reported<sup>6</sup> the natural product to be 7-hydroxy-5-methoxyphthalide (III), a compound previously synthesised by Allison and Newbold.<sup>7</sup>



(III)

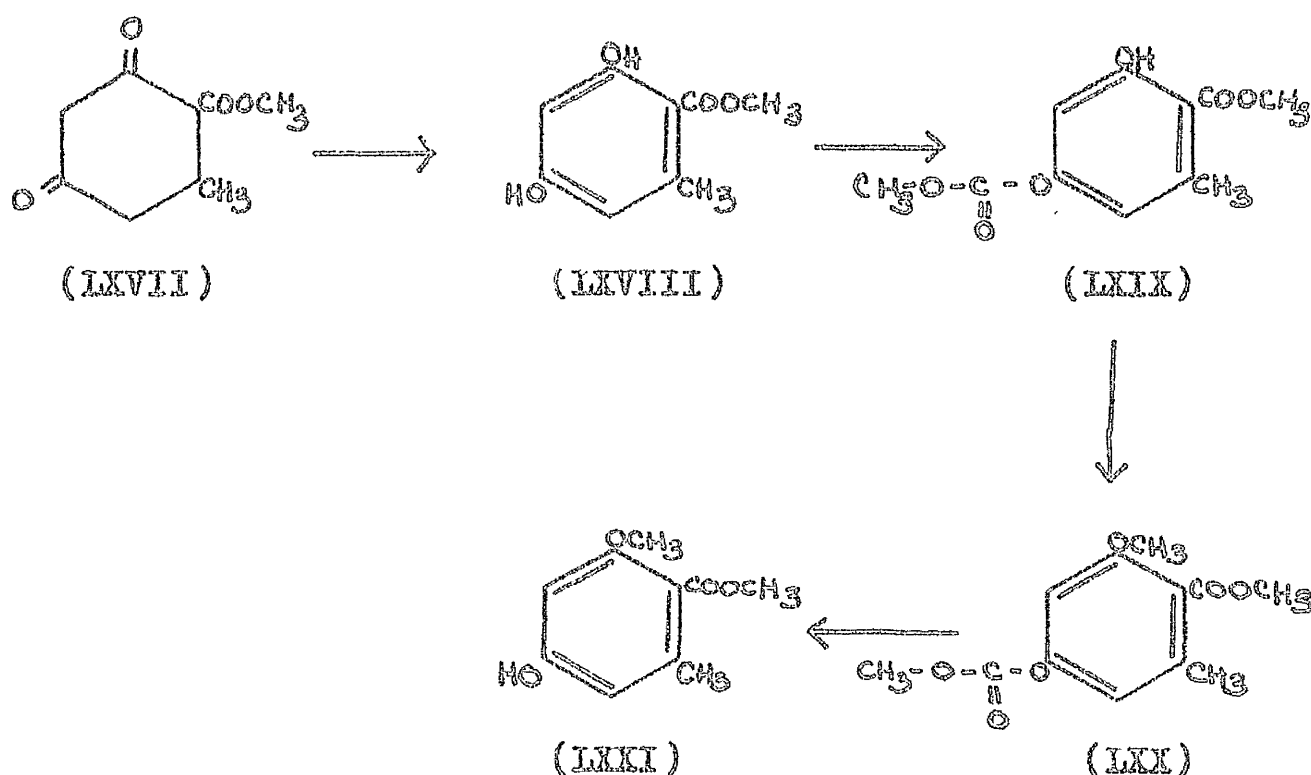
### Synthesis of 5-Hydroxy-7-methoxyphthalide (LXVI)

Methyl 1-methyl-3,5-dioxocyclohexane-2-carboxylate (LXVII), prepared<sup>51</sup> from methyl acetoacetate and methyl crotonate, was converted to methyl 4,6-dihydroxy-2-methylbenzoate (LXVIII) by aromatisation with anhydrous ferric chloride in acetic acid.<sup>52</sup>

In phenolic esters of this type, due to the existence of strong intramolecular hydrogen-bonding between the 6-hydroxyl group and the ester group in the ortho position to it, the 6-hydroxyl group is much less reactive than that in the 4-position. The latter group may be acylated and methylated under normal reaction conditions while the former reacts very much more slowly. The difference in reactivity has been widely used in the preparation of monoethers and monoesters where attack is found to take place exclusively on the 4-hydroxyl group. To methylate the 6-hydroxyl therefore, it is necessary first to block the 4-hydroxyl group with some easily removable substituent.

With a view to blocking the 4-hydroxyl group in (LXVIII), the compound was treated with freshly distilled methyl chloroformate at room temperature according to the method of Fischer and Hoesch<sup>53</sup> and yielded methyl 3-hydroxy-4-methoxycarbonyl-5-methylphenyl carbonate (LXIX)

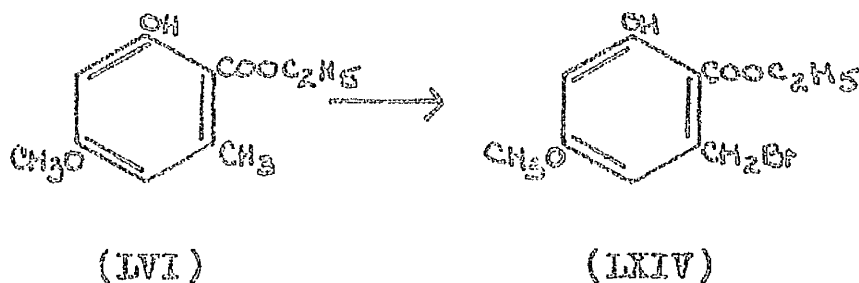
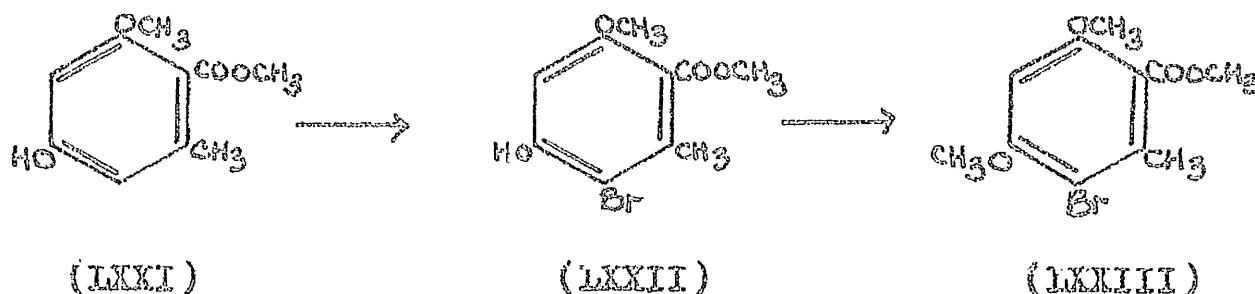
in moderate yield. On prolonged treatment with diazo-methane in ether, (LXIX) gave methyl 3-methoxy-4-methoxy-carbonyl-5-methylphenyl carbonate (LXX). Methyl 4-hydroxy-6-methoxy-2-methylbenzoate (methyl isoeverninate) (LXXI) was obtained in good yield by hydrolysis of (LXX) with aqueous methanolic sodium hydroxide at room temperature.



On photobromination, (LXXI) readily took up one mol. of bromine to give methyl 3-bromo-4-hydroxy-6-methoxy-2-methylbenzoate (LXXII). The photobromination, like all others in this work, was carried out by the method of Eliel *et al.*<sup>36,37</sup>. A solution of the material in dry

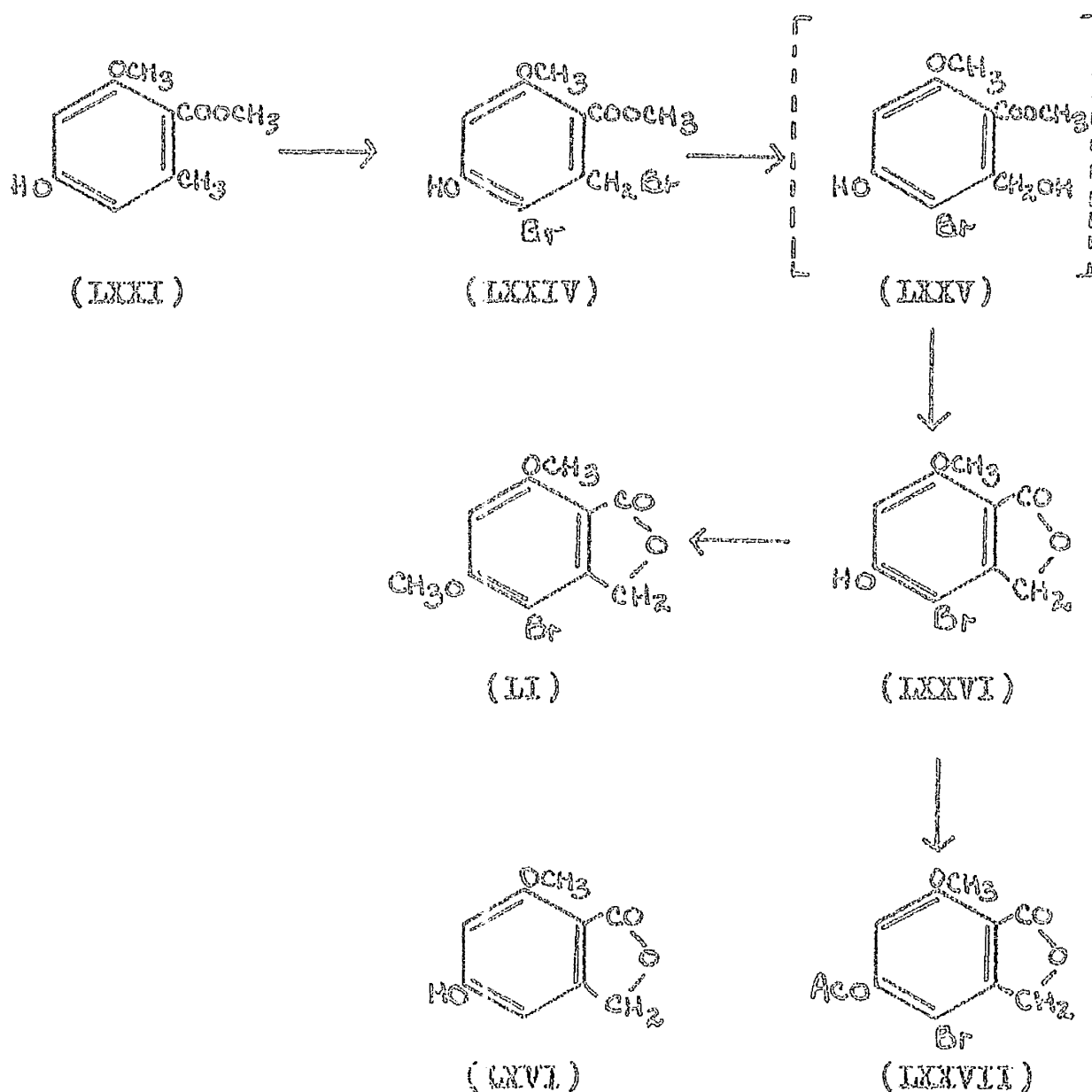
carbon tetrachloride in a quartz flask was gently refluxed by irradiation from a 150W. tungsten filament lamp. The stoichiometric amount of a solution of bromine in dry carbon tetrachloride was added dropwise to the refluxing solution, each addition being made only after the colour of the previous addition had almost disappeared.

The structure of (LXXII) was confirmed by its ready conversion on treatment with ethereal diazomethane to methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate (LXXIII), previously prepared by Logan and Newbold.<sup>47</sup>



The position of substitution of the bromine on photo-monobromination of (LXXI) is in direct contrast to the findings of Allison and Newbold<sup>7</sup> on photo-monobromination of ethyl 6-hydroxy-4-methoxy-2-methylbenzoate (ethyl everninate) (LVI) under identical conditions. In the latter case substitution of bromine took place in the methyl side-chain yielding ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (LXIV). It seems likely that the difference in point of substitution is due to steric factors. The 4-hydroxyl group occupies less space than the more bulky 4-methoxyl group and thus the large bromine atom can more readily substitute in the 3-position of the methyl isoeverninate molecule than in the corresponding position in ethyl everninate (LVI).

On photo-dibromination of methyl isoeverninate (LXXI) under identical conditions methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate (LXXIV) was obtained in good yield. Hydrolysis of (LXXIV), achieved by refluxing the compound in aqueous dioxan gave 4-bromo-5-hydroxy-7-methoxyphthalide (LXXVI) in 89% yield. This form of mild hydrolysis has been used repeatedly in this work for the hydrolysis of compounds containing side-chain bromine substituents, although the solvent:water ratio and the duration



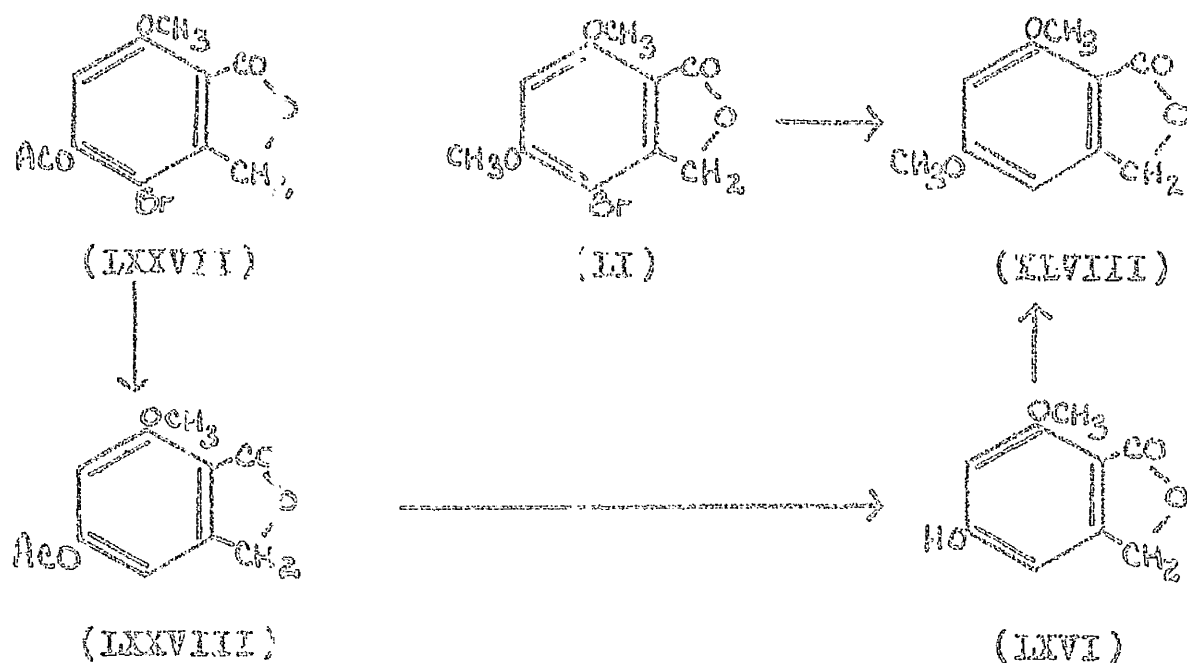
of reflux vary widely. In this case the solution was refluxed for 44 hours with a solvent : water ratio of 3:2. The reaction may be considered to have proceeded through the intermediate hydroxymethyl derivative (LXXV) which was

not isolated. Hydrogen bromide liberated in the first stage acts as a catalyst in the completion of the hydrolysis and allows lactonisation to take place. The structure of (LXXVI) and hence also of (LXXIV) was confirmed by conversion of the bromo-phthalide to 4-bromo-5,7-dimethoxy-phthalide (LI), previously prepared by Logan and Newbold.<sup>47</sup> 4-Bromo-5-hydroxy-7-methoxyphthalide (LXXVI) was also readily converted to 5-acetoxy-4-bromo-7-methoxyphthalide (LXXVII) by heating the former compound in acetic anhydride containing concentrated sulphuric acid (1 drop).

Repeated attempts were unsuccessfully made to convert 4-bromo-5-hydroxy-7-methoxyphthalide (LXXVI) dissolved in dry ethyl acetate, to 5-hydroxy-7-methoxyphthalide (LXVI) by shaking the solution in the presence of palladised charcoal and magnesium oxide in an atmosphere of hydrogen at room temperature for various periods up to 60 hours. On replacement of the palladised charcoal with pre-reduced Adams' catalyst, debromination still did not take place. The great insolubility of the bromo-phthalide in ethyl acetate necessitated the use of a solution of very low solute concentration.

It would seem that this factor is responsible for the failure of the reaction. This theory is borne out by the

fact that 4-bromo-5,7-dimethoxyphthalide (LI) which had previously been found<sup>47</sup> to be easily convertible to 5,7-dimethoxyphthalide (XLVIII) would not react at the same dilution and under otherwise identical conditions to those used in the case of (LXXVI).



5-Acetoxy-4-bromo-7-methoxyphthalide (LXXVII), which was found to be very much more soluble in ethyl acetate than 4-bromo-5-hydroxy-7-methoxyphthalide (LXXVI), was converted in good yield to 5-acetoxy-7-methoxyphthalide (LXXVIII) on shaking its ethyl acetate solution in a hydrogen atmosphere at room temperature in the presence of



pre-reduced Adams' catalyst and magnesium oxide. Alkaline hydrolysis of 5-acetoxy-7-methoxyphthalide (LXXVIII) at steam-bath temperature yielded 5-hydroxy-7-methoxyphthalide (LXVI). Confirmation of the structure of the hydrolysis product was obtained by its conversion with ethereal diazomethane to the previously prepared<sup>47</sup> 5,7-dimethoxyphthalide (XLVIII).

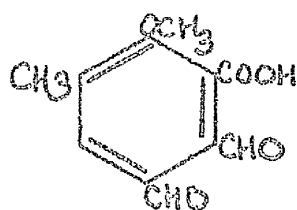
The physical constants and infrared data reported<sup>6</sup> by Herout et al. were entirely different from those found for 5-hydroxy-7-methoxyphthalide (LXVI) but were in complete agreement with those published by Allison and Newbold<sup>7</sup> for 7-hydroxy-5-methoxyphthalide (III).

#### Outline of Possible Routes to Cyclopaldic Acid (VIII)

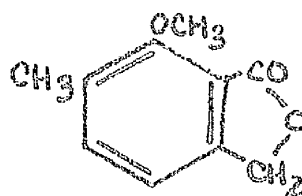
Although fairly conclusive evidence has been put forward<sup>14</sup> in support of the proposed structure of cyclopaldic acid (VIII) from degradative experiments on the natural product, no total synthesis has so far been reported. Possible synthetic routes to the acid (VIII) have therefore been investigated.

In the syntheses of gladiolic acid (X) as described in the Introduction, the desired product was obtained from 7-methoxy-6-methylphthalide (LXXIX) by either of two elegant methods.<sup>26,27,28,29</sup> The initial objective of the

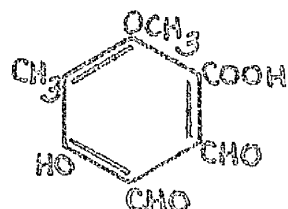
investigation, therefore, was the development of a synthesis of 5-hydroxy-7-methoxy-6-methylphthalide (LXXX), the corresponding precursor of cyclopaldic acid (VIII). Before commencing work on the synthesis of 5-hydroxy-7-methoxy-6-methylphthalide (LXXX), however, a parallel synthesis of the isomeric 7-hydroxy-5-methoxy-6-methylphthalide (LXXXI) was attempted in which the feasibility of various intermediate reactions in the planned route to 5-hydroxy-7-methoxy-6-methylphthalide (LXXX) was examined using more readily available starting materials.



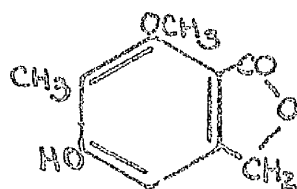
(X)



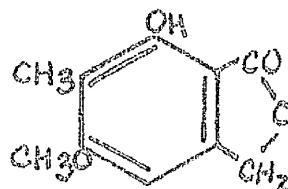
(LXXIX)



(VIII)



(LXXX)



(LXXXI)

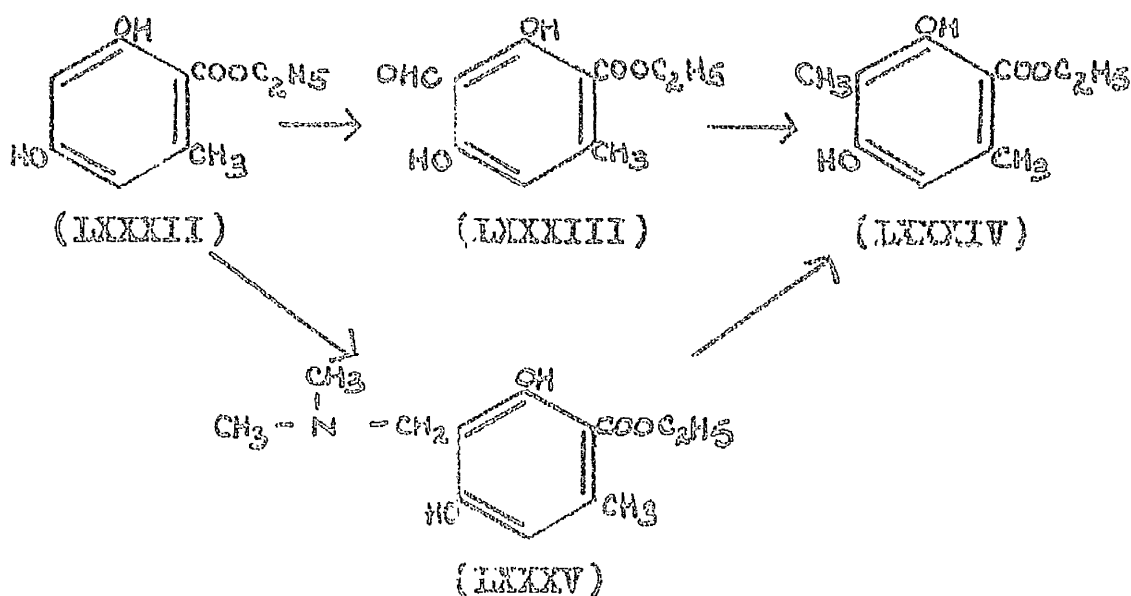
Synthetic Routes to 7-Hydroxy-5-methoxy-6-methylphthalide  
(LXXXI)

The choice of which ester series is the more suitable for any particular synthesis is determined largely by the amount of previous work done on the intermediate compounds in each case. In this instance the ethyl ester was used.

Ethyl 2,4-dihydroxy-6-methylbenzoate (ethyl orsellinate) (LXXXII), prepared in two stages<sup>51, 52</sup> from ethyl crotonate and ethyl acetoacetate in an analogous manner to the corresponding methyl ester (LXVIII), was converted in high yield to ethyl 2,4-dihydroxy-3-formyl-6-methylbenzoate (ethyl haematommate) (LXXXIII) by the Gattermann Reaction as modified by Whalley.<sup>54</sup>

Reduction of (LXXXIII) to ethyl 2,4-dihydroxy-3,6-dimethylbenzoate (ethyl  $\beta$ -orcinol carboxylate) (LXXXIV) by means of the Clemmensen Reaction<sup>54</sup> proceeded in very low yield. In order to form an organic layer immiscible with the aqueous phase, toluene was used to replace ethanol in a subsequent experiment and the reflux time was extended to 40 hours. A very low yield (c. 25%) of ethyl  $\beta$ -orcinol carboxylate (LXXXIV), together with a high yield of unchanged material, was once more obtained. Preparation of (LXXXIV) from ethyl haematommate (LXXXIII) was carried out in high yield by shaking the latter compound, dissolved in

glacial acetic acid, in an atmosphere of hydrogen at room temperature and atmospheric pressure in the presence of pre-reduced Adams' catalyst. This method of reduction, however, required relatively large quantities of catalyst. The optimum yield of product (73%) was obtained on using 7 parts of catalyst to 10 parts of ethyl haematommate (LXXXIII). On lowering the ratio of catalyst to reduceable material to 1:2 the yield of ethyl  $\beta$ -orcinol carboxylate (LXXXIV) dropped to 45%. Using still less catalyst the yield of reduced material dropped off rapidly.



An alternative route to ethyl  $\beta$ -orcinol carboxylate (LXXXIV) from ethyl orsellinate (LXXXII) involved the formation of ethyl 2,4-dihydroxy-3-dimethylaminomethyl-6-methylbenzoate (LXXXV) from (LXXXII) by the Mannich

Reaction. In this preparation the latter compound was refluxed with bis(dimethylamino)methane in a nitrogen atmosphere. The benzylamine derivative, (LXXXV), was converted to the corresponding toluene derivative, ethyl  $\beta$ -orcinol carboxylate (LXXXIV) on hydrogenation in glacial acetic acid solution at 95° and atmospheric pressure in the presence of palladised charcoal (10% Pd). When the duration of hydrogenation was extended beyond 20 hours the yield of reduced material diminished. An unidentified colourless oil was isolated from the reaction in such cases. Micro-analytical data on the oil indicated that the aromatic ring had suffered hydrogenation.

The overall yield of ethyl  $\beta$ -orcinol carboxylate (LXXXIV) from ethyl orsellinate was exactly the same by one route as by the other (51.5%). The main factor favouring the route via the dimethylaminomethyl compound (LXXXV) was the economy achieved in catalyst consumption.

Ethyl 3,6-dimethyl-2-hydroxy-4-methoxybenzoate<sup>55</sup> (ethyl rhizonate) (LXXXVI) was obtained by the brief action of ethereal diazomethane on ethyl  $\beta$ -orcinol carboxylate (LXXXIV). Attack took place preferentially on the more reactive 4-hydroxyl in the relatively short time allowed for reaction.

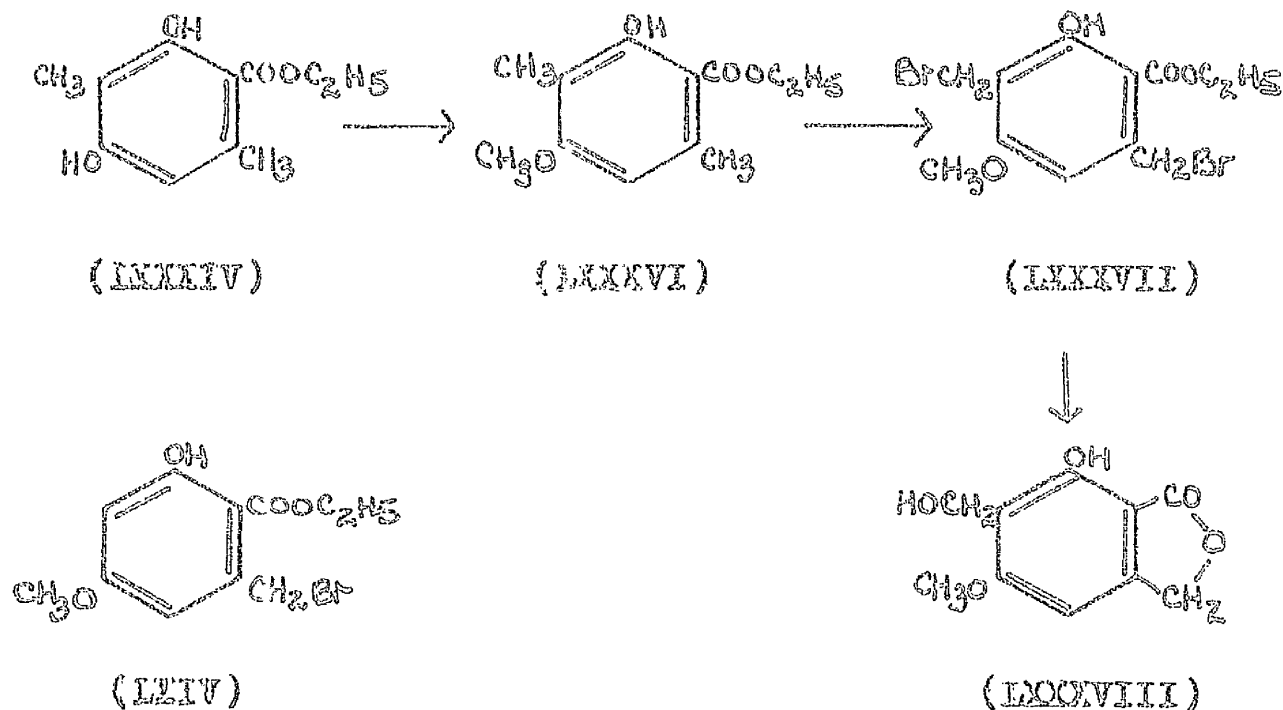


Photo-bromination of (LXXXVI) yielded a dibromide in moderate yield. In this compound it was considered that one bromine atom might have substituted in the free nuclear position and one in the side chain, or both side chains might have been substituted. A third less likely possibility could have been disubstitution of one side chain. Hydrolysis of the dibromide to 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) proved the compound to be ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII). The substitution of both bromine atoms on the side chain methyl groups during photo-bromination under dry conditions is in agreement with the findings of Allison and

Newbold<sup>7</sup> in the synthesis of ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (LXIV). The mode of bromination in both cases contradicts the theory of Logan and Newbold<sup>47</sup> in which they stated that nuclear bromination must occur first and the presence of the ortho-bromo-group is necessary to activate the methyl group for side-chain bromination.

Conversion of ethyl 2,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII) to 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) was achieved by the aqueous dioxan method, a reflux time of 30 hr. and a solvent : water ratio of 4:1 being employed. Under these conditions the yield of crystalline product from the reaction was very poor and a large amount of an uncrystallisable brown oil was obtained, which showed phthalide carbonyl absorption at  $1736\text{ cm.}^{-1}$ , identical in value with that shown by the pure crystalline phthalide. Further treatment of the oil under the previous reaction conditions, however, failed to produce crystalline material.

The hydrolysis of (LXXXVII) involved the liberation of two molecules of hydrogen bromide per molecule of phthalide formed. In other hydrolyses by this method, previously reported,<sup>7</sup> only one molecule of hydrogen bromide was liberated per molecule of phthalide. It seems possible

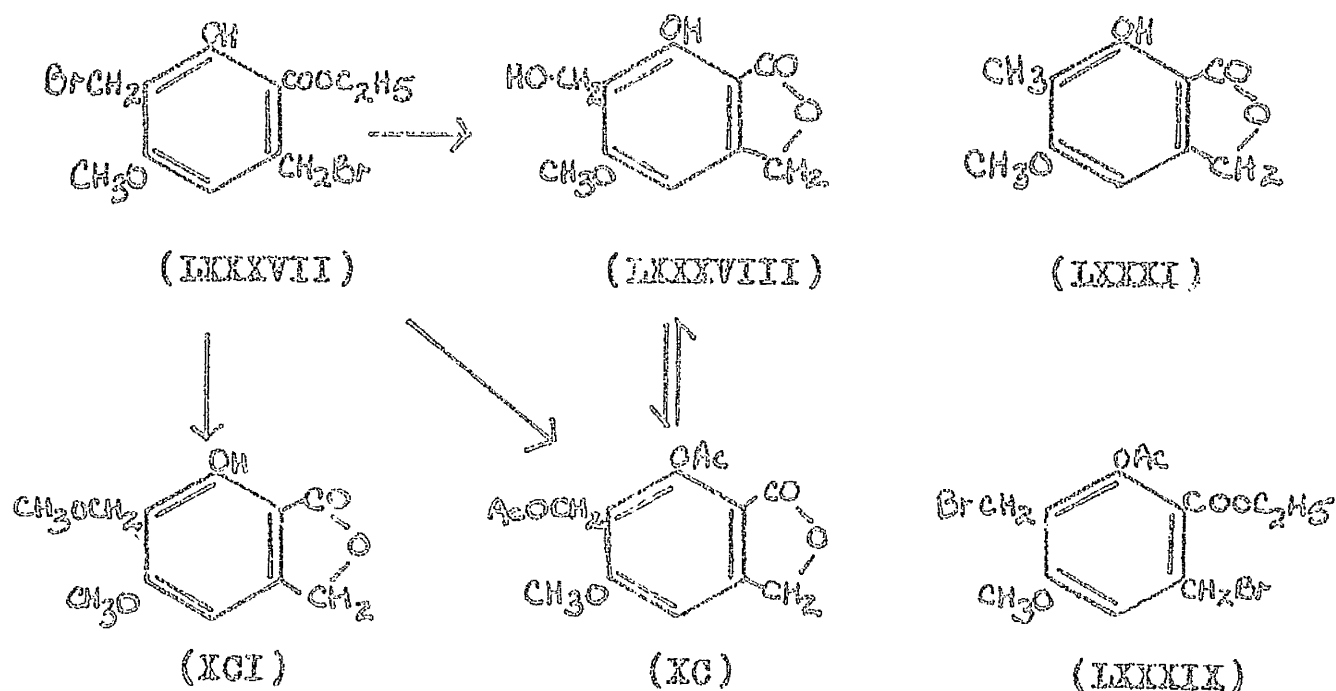
that in this case the excess hydrogen bromide in the aqueous medium exerted a detrimental effect on the hydrolysis product. The hydrolysis was attempted using a very much shorter reaction time (6 hours) but the yield of crystalline material was not improved.

A somewhat higher yield of 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) (38%) was obtained on refluxing the dibromide (LXXXVII) for 20 hours in aqueous acetone.

In order to eliminate the possibility of any side reaction involving the 2-hydroxy group taking place on hydrolysis, it was decided to attempt to convert ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII) to ethyl 2-acetoxy-3,6-di(bromomethyl)-4-methoxybenzoate (LXXXIX). It was hoped that subsequent hydrolysis and lactonisation would then proceed in higher yield. On refluxing (LXXXVII) in acetic anhydride, 7-acetoxy-6-acetoxymethyl-5-methoxyphthalide (XC) was isolated in moderate yield.

Treatment of 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) with acetic anhydride containing catalytic amounts of concentrated sulphuric acid also yielded 7-acetoxy-6-acetoxymethyl-5-methoxyphthalide (XC).





Hydrolysis of the latter compound in 1N. sodium hydroxide returned 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) in good yield. Thus by acetylation of ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII) and subsequent hydrolysis of the phthalide acetate (XC), it is possible to prepare 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII) by an alternative route to that previously described. However, proceeding through the acetate a 28% yield of (LXXXVIII) from (LXXXVII) was obtained, lower by 10% than that obtained by use of the aqueous acetone method.

In a further attempt to find means of hydrolysing (LXXXVII) in higher yield the compound was refluxed for

12 hrs. in aqueous methanol and 7-hydroxy-5-methoxy-6-methoxymethylphthalide (XCI) was isolated.

An initial attempt to obtain 7-hydroxy-5-methoxy-6-methylphthalide (LXXXI) by hydrogenation of (LXXXVIII) at atmospheric pressure and room temperature in the presence of pre-reduced Adams' catalyst was unsuccessful.

At this point work on this series was discontinued and efforts were concentrated on a synthesis of 5-hydroxy-7-methoxy-6-methylphthalide (LXXX).

#### Synthetic Routes to 5-Hydroxy-7-methoxy-6-methylphthalide (LXXX)

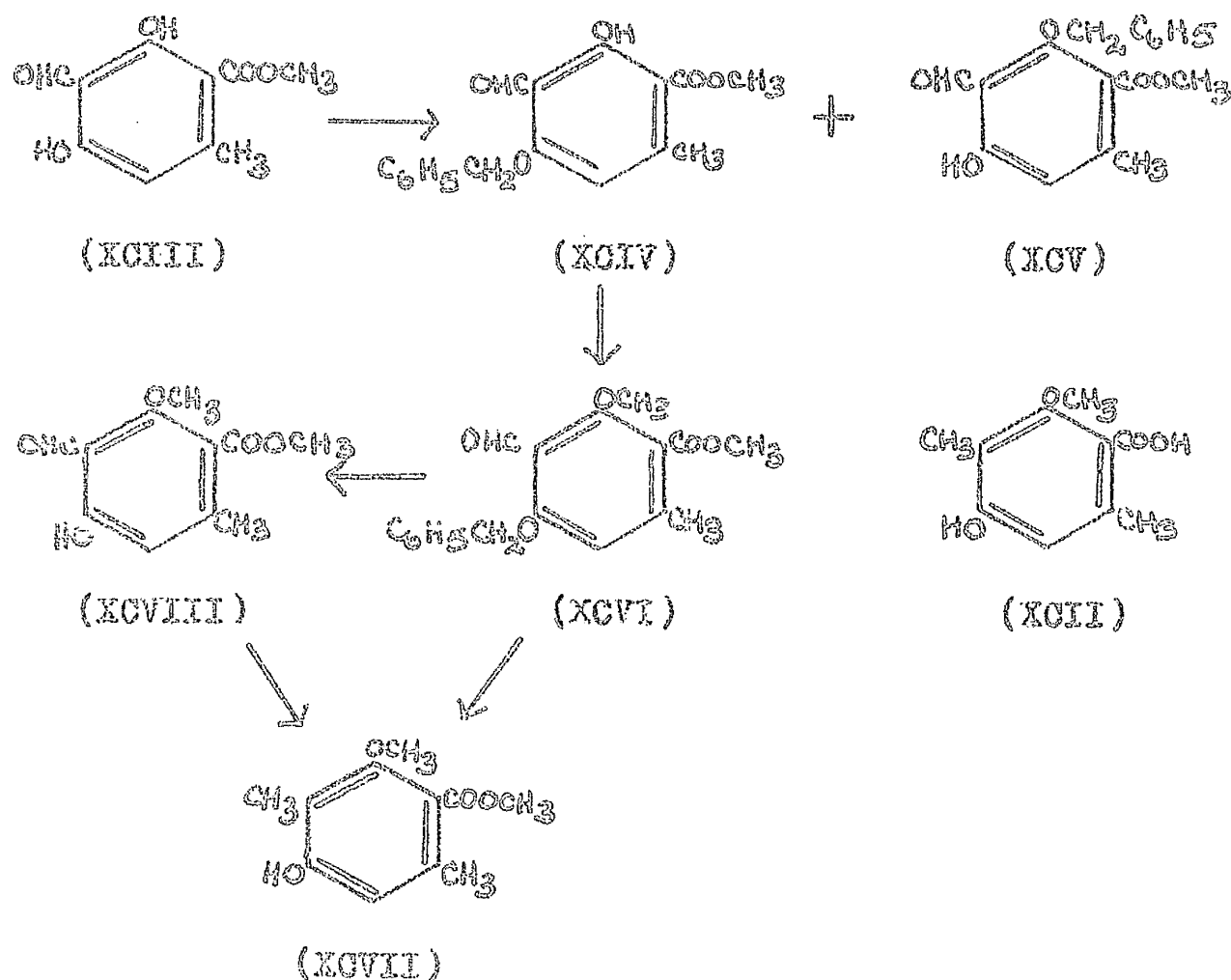
In the first route devised for the synthesis of 5-hydroxy-7-methoxy-6-methylphthalide (LXXX) the initial problem was that of synthesising either the methyl or ethyl ester of 3,6-dimethyl-4-hydroxy-2-methoxybenzoic acid (isorhizonic acid) (XCII). Two previous syntheses of methyl isorhizonate (XCVII) have been reported, one of which<sup>56, 57</sup> involved a total of twelve consecutive reactions. Since (XCVII) was required as starting material for a further lengthy synthesis this route was not re-examined. The second synthesis considered was that reported by Asahina and Shibata.<sup>58</sup> Although no yield of pure product was given by these authors for any of the reactions

involved, the synthesis was re-investigated. Methyl haematommate (XCIII), prepared in the manner described for the ethyl ester<sup>51, 52, 54</sup> (LXXXIII), was refluxed with benzyl chloride and potassium carbonate in acetone. A mixture of methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate (XCIV) and methyl-2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (XCV) was obtained, in which the latter compound was the major component. The materials were separated cleanly by utilising differences in their solubility in aqueous sodium hydroxide solution. In the case of (XCIII), in addition to the intramolecular hydrogen-bonding which might be expected to exist between the ester group and the 2-hydroxyl, similar bonding must exist between the 3-formyl group and the 2- and 4-hydroxyl groups. From these considerations it may be seen that no marked difference in reactivity might be expected between the hydroxyl groups in this compound. For this reason, the 4-hydroxyl group could not be benzylated preferentially.

Methylation of methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate (XCIV) with methyl iodide and potassium carbonate yielded methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (XCVI) in moderately good yield. The latter compound, however, was hydrogenated in the presence of palladised charcoal (10% Pd) in very poor yield to methyl

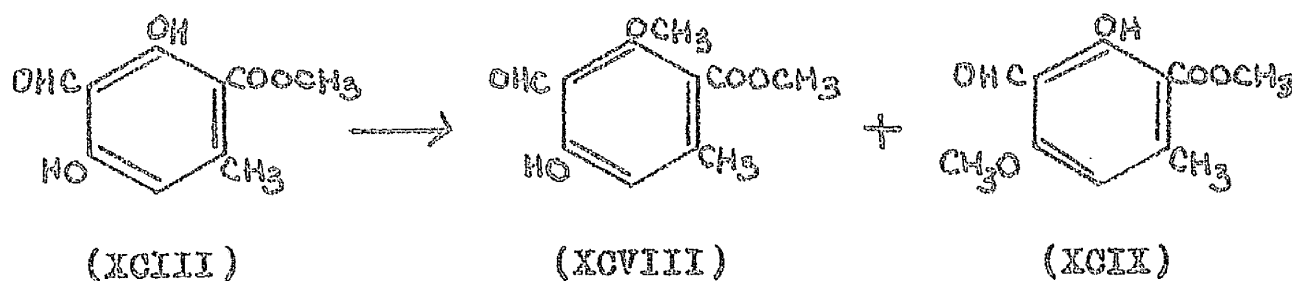
isorhizonate (XCVII). On repeating the reaction in the presence of palladised charcoal (20% Pd) in an otherwise identical manner the yield was somewhat higher (27%). No improvement on the former yield could be obtained on using pre-reduced Adams' catalyst.

The poor yield from the hydrogenation coupled with the low yield of methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate (XCIV) (25%) from the benzylation rendered this scheme of reactions unsuitable for the synthesis of methyl isorhizonate (XCVII).

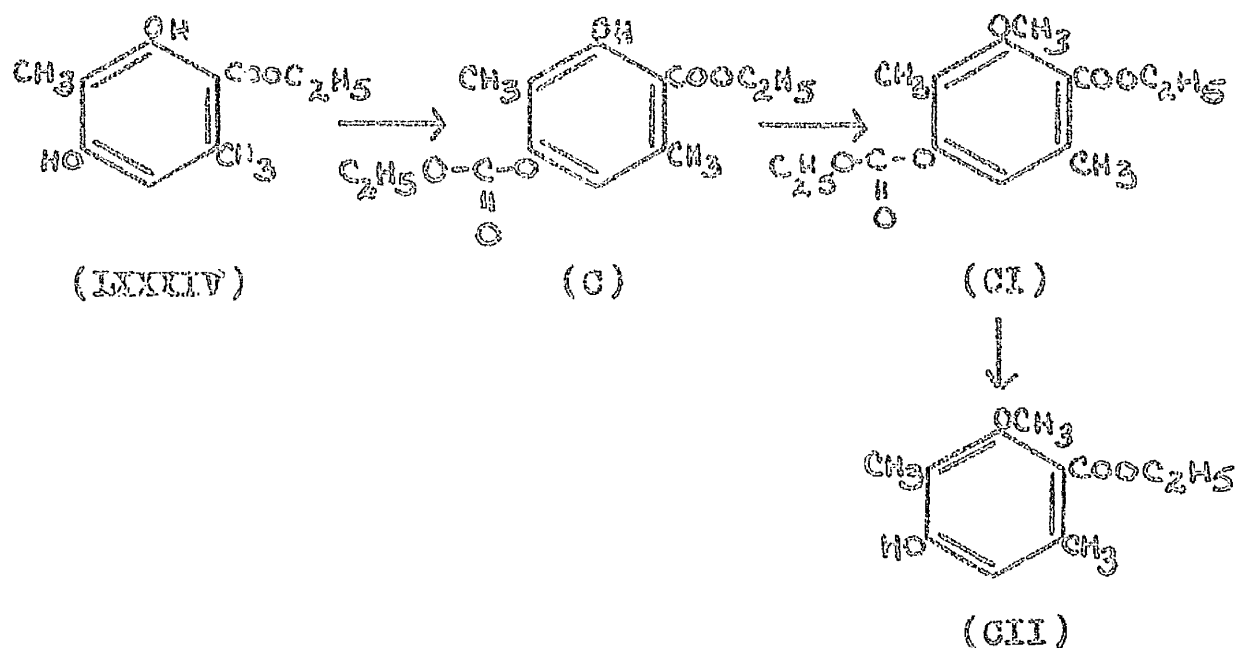


Debenzylation of methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (XCVI), carried out by the literature method<sup>58</sup> yielded methyl 3-formyl-4-hydroxy-2-methoxy-6-methylbenzoate (XCVIII) which on hydrogenation in the presence of palladised charcoal (10% Pd) furnished methyl isorhizonate (XCVII) in good yield. (XCVII) was obtained by the latter route from methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (XCVI) in an overall yield of 41%, somewhat better than that obtained by direct hydrogenation.

Although from previous reasoning, a mixture of the monomethyl ethers (XCVIII) and (XCIX) was to be expected, direct mono-methylation of methyl haematommate (XCIII) with methyl iodide and the theoretical amount of potassium carbonate in acetone was attempted in the hope that some suitable means of purification of the mixture might be found. No straightforward separation was possible and after laborious fractional recrystallisation only a partial separation was achieved.



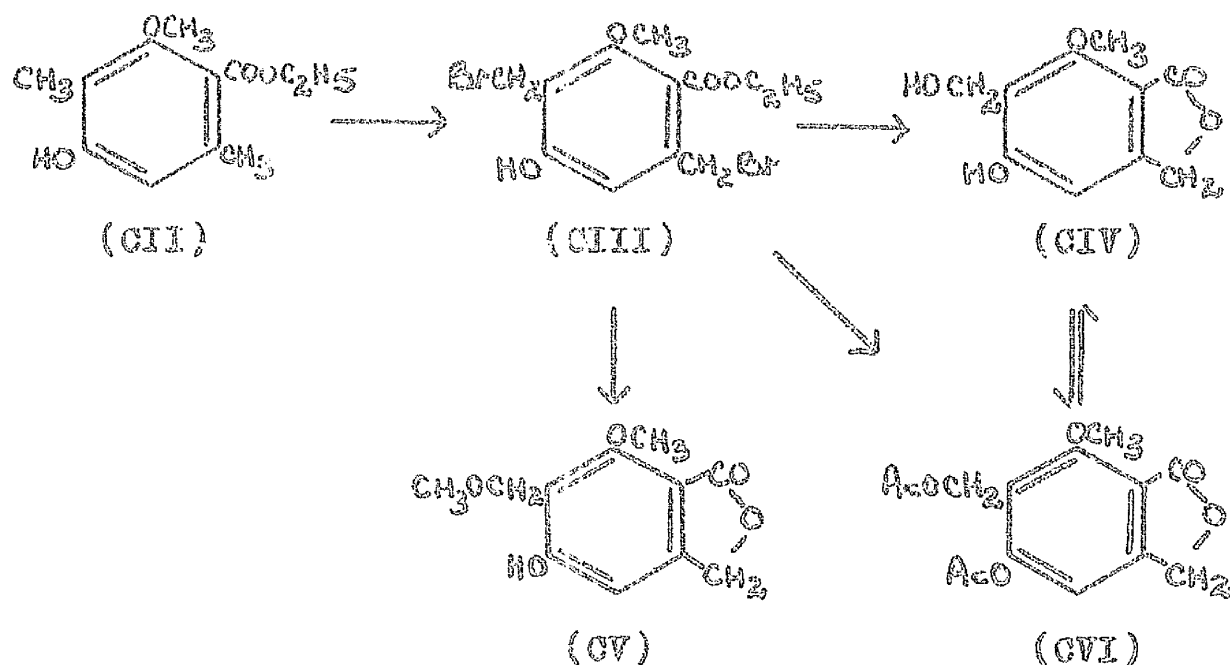
A synthesis of ethyl isorhizonate (CII) was developed in substantially higher yield from ethyl  $\beta$ -orcino] carboxylate (LXXXIV), prepared by the method previously described. As in the isoeverninate series, it was necessary to protect the 4-hydroxyl group prior to methylating the one in the 2-position. To fulfil this requirement ethyl  $\beta$ -orcino] carboxylate (LXXXIV) was treated at room temperature with ethyl chloroformate in alkali. Ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-hydroxyphenyl carbonate (C) was obtained. Treatment of (C) with ethereal diazomethane yielded a good return of ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-methoxyphenyl carbonate (CI) as a colourless oil, which was hydrolysed directly to ethyl isorhizonate (CII) with aqueous ethanolic sodium hydroxide. Hydrolysis of



the products claimed to be ethyl isorhizonate (CII) and methyl isorhizonate (XCVII) yielded the well characterised isorhizonic acid (XCII) in low yield in both cases, thereby confirming the authenticity of the materials.

Photo-dibromination of (CII) gave ethyl 3,6-di(bromo-methyl)-4-hydroxy-2-methoxybenzoate (CIII) in 41% yield. The crude product at the end of the reaction was in the form of a viscous brown oil and great care in the subsequent crystallisation was required to achieve the stated yield of pure crystalline dibromide. A large amount of uncrystallisable brown oil was obtained from the mother liquors. On recrystallisation it was observed that a relatively large amount of material was lost when undried commercial solvent was used. It is thought that this was due to partial decomposition of the compound in the presence of water by residual traces of hydrogen bromide in the boiling solution. Using specially dried solvent a cleaner product was obtained without appreciable loss of material. No completely satisfactory analysis values were obtained, however. This was undoubtedly associated with the difficulty of preparing an absolutely pure sample of the compound. The values were sufficiently close to those calculated for the dibromide to establish the molecular

formula beyond doubt. The structure of the dibromide was confirmed to be ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (CIII) by its conversion on hydrolysis to 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV).



The hydrolysis was initially attempted by the aqueous dioxan method. High melting point amorphous material, insoluble in organic solvents, was isolated but not identified. On repeating the experiment with a much shorter reflux time, a brown oil was obtained which displayed the characteristic phthalide absorption band in the infrared region, but from which no crystalline material could be obtained.

5-Hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV)

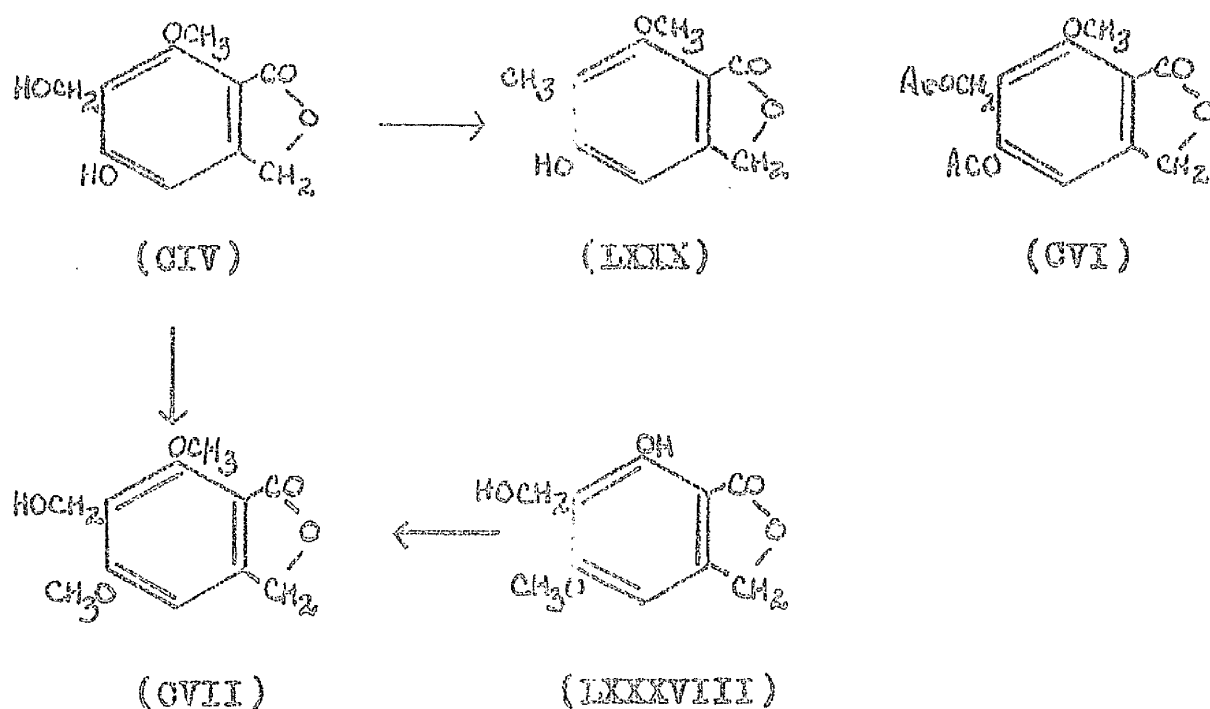


was obtained in 68% yield on refluxing (CIII) for  $5\frac{1}{2}$  hr. in aqueous acetone. Also, on refluxing (CIII) with aqueous methanol for  $8\frac{1}{2}$  hr., 5-hydroxy-7-methoxy-6-methoxymethyl-phthalide (CV) was isolated.

The action of acetic anhydride under reflux conditions on ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (CIII) was similar to that on the isomeric ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII), the corresponding phthalide diacetate, 5-acetoxy-6-acetoxymethyl-7-methoxyphthalide (CVI), being isolated. The same compound was obtained by the action of acetic anhydride containing catalytic quantities of concentrated sulphuric acid, on 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV). The latter compound was readily regenerated from the diacetate (CVI) in good yield by the action of 1N. sodium hydroxide. Thus, in this series also an alternative route from (CIII) to (CIV) exists through (CVI). However the high yield of (CIV) obtained from (CIII) on hydrolysis with aqueous acetone, renders the alternative route less attractive.

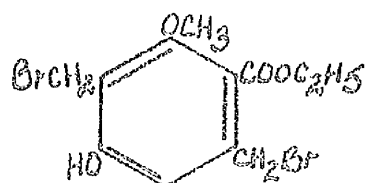
Hydrogenation of 5-acetoxy-6-acetoxymethyl-7-methoxyphthalide (CVI) was attempted firstly in ethyl acetate at room temperature and secondly in glacial acetic acid at  $95^{\circ}$ ,

in both cases in the presence of pre-reduced Adams' catalyst. Unchanged material was isolated in high yield in both cases. 5-Hydroxy-7-methoxy-6-methylphthalide (LXXX) was obtained in 43% yield by hydrogenation of 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV) in glacial acetic acid at 95° in the presence of pre-reduced Adams' catalyst.

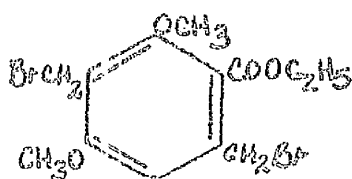


The treatment of 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV) with ethereal diazomethane for 12 hr. yielded 5,7-dimethoxy-6-hydroxymethylphthalide (CVII) which was also obtained by similar treatment of 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (LXXXVIII). Attempts to prepare ethyl 3,6-di(bromomethyl)-2,4-dimethoxybenzoate

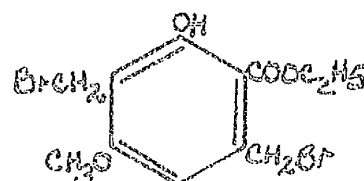
(CVIII) by similar treatment of ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (CIII) and ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (LXXXVII) with ethereal diazomethane were unsuccessful. This was thought to be due to steric hindrance occasioned by the presence in both cases of the large bromo-methyl group in the *ortho*-position to the hydroxyl group which it was desired to methylate.



(CIII)



(CVIII)

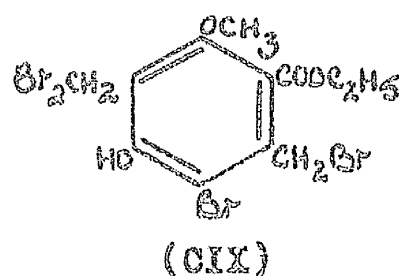
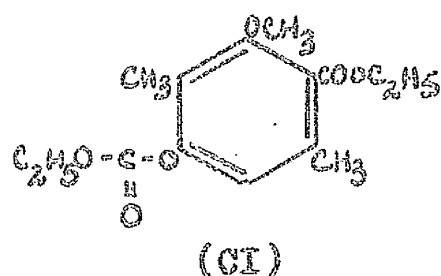


(LXXXVII)

In an effort to eliminate a stage in the synthesis an attempt was made to photo-dibrominate ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-methoxyphenol carbonate (CI); a brown gum differing in infrared spectrum from the carbonate (CI), was obtained. The gum, which could not be crystallised, was treated directly with aqueous acetone under reflux for 24 hr. No crystalline material was obtained.

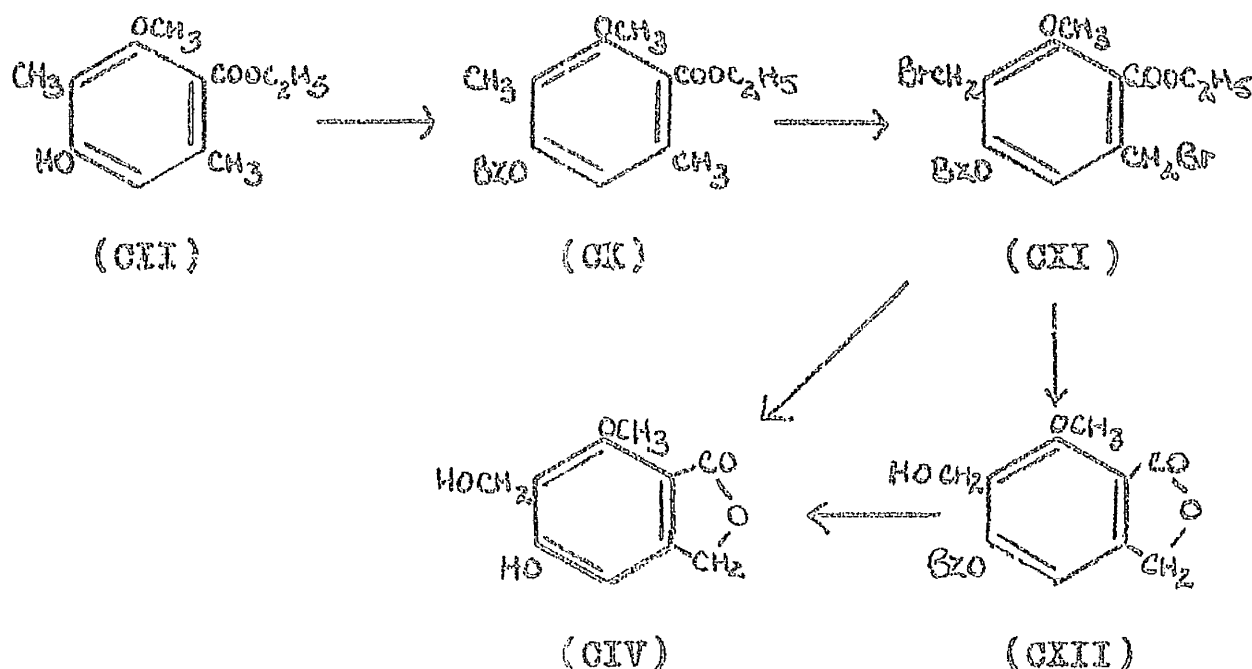
Photo-tribromination of ethyl isorhizonate (CII) gave a very small yield of a tribromide, likely to be ethyl 5-bromo-3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (CIX). In this case, a large quantity of uncrystallisable oil was also

isolated. As in the case of the corresponding dibromide (CIII) no satisfactory analysis values were obtained for the crystalline material. However, the values obtained definitely showed the material to contain three bromine atoms in the molecule. On refluxing the oil and crystalline material separately in aqueous acetone for 24 hr. no crystalline material was obtained in either case, and thus the suggested structure of the tribromide could not be confirmed.



With a view to improving, if possible, the yield in the bromination and hydrolysis reactions in this series, a benzoyl group was substituted in the 4-position of the ethyl isorhizonate molecule. Ethyl 4-benzoyloxy-3,6-dimethyl-2-methoxybenzoate (CX) was prepared from ethyl isorhizonate (CII) in good yield by the action of benzoyl chloride in pyridine. Photo-dibromination of (CX) took place in 48% yield to give ethyl 4-benzoyloxy-3,6-di(bromomethyl)-2-methoxybenzoate (CXI), the structure of which was confirmed by formation of 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide

(CIV) on hydrolysis. The latter reaction was carried out by refluxing the dibromide in aqueous dioxan for 22 hr., and the product was obtained in 43% yield. A very low yield (11%) of 5-benzoyloxy-6-hydroxymethyl-7-methoxyphthalide (CXII) was also obtained. The latter compound was obviously an intermediate in the formation of (CIV) and was readily hydrolysed to (CIV) in alkaline solution.

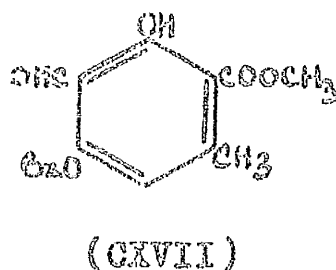
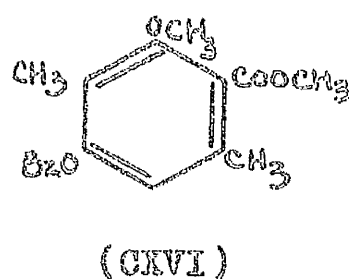
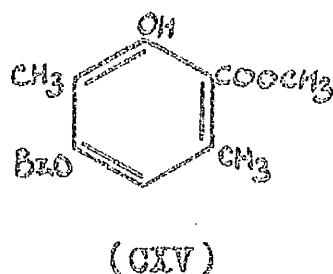
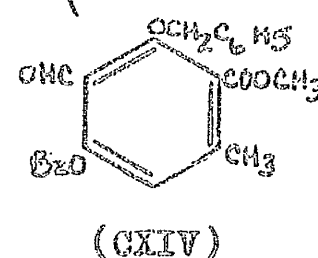
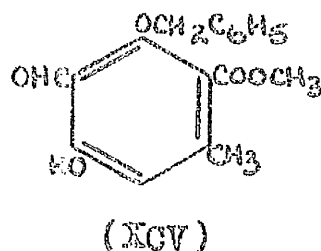
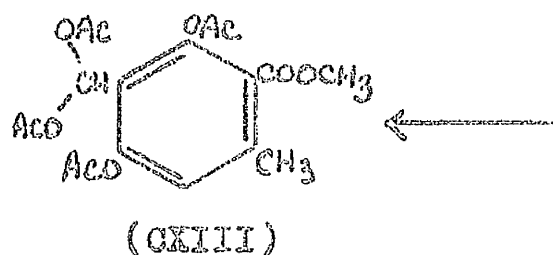
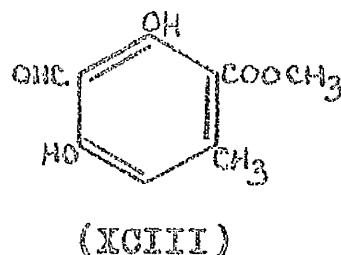
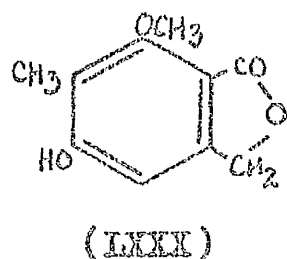


The series of reactions just described constitutes a third synthetic route to 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (CIV) from ethyl isorhizonate (CI). However, due to the extra stage involved and the moderate yields obtained this route is in no way preferable to the direct one involving dibromination and aqueous acetone hydrolysis.

The major product obtained on benzylation of methyl haematommate (XCIII) was methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (XCV) and thus an attempt was made to develop a synthetic route to 5-hydroxy-7-methoxy-6-methylphthalide (LXXX) from (XCV). In order to obtain at a later stage a high yield of product preferentially methylated in the 2-position it appeared necessary to block the 4-hydroxyl group before attempting to remove the benzyl group. Since it was considered that an acyl group substituted on the 4-hydroxyl position could be easily removed at a later stage, formation of the 4-acetoxy derivative was attempted by heating (XCV) at 100° with acetic anhydride containing a catalytic quantity of concentrated sulphuric acid. Methyl 2,4-diacetoxy-3-diacetoxymethyl-6-methylbenzoate (CXIII) was isolated. Under the acid conditions debenylation had obviously taken place initially. The occurrence of an absorption band in the infrared at 1799  $\text{cm.}^{-1}$  in Nujol confirmed that diacetylation of the 3-formyl group had taken place also. (CXIII) was clearly of no value to the furtherance of the proposed synthesis. Treatment of (XCV) with acetic anhydride and pyridine at 100° yielded unchanged material in high yield.

On treatment of (XCV) with benzoyl chloride and pyridine at 100°, methyl 4-benzoyloxy-2-benzyloxy-3-formyl-

6-methylbenzoate (CXIV) was obtained in good yield.



It was hoped that hydrogenation of (CXIV) might convert the 3-formyl group to a methyl group and remove the 2-benzyl group simultaneously, thereby producing (CXV). Methylation

of the 2-hydroxyl group would then yield (CXVI). It was planned to convert this material to 5-hydroxy-7-methoxy-6-methylphthalide (LXXX) in a similar manner to that employed with the corresponding ethyl ester (CX). However, on attempting the hydrogenation of (CXIV) in ethyl acetate at room temperature in the presence of palladised charcoal (20% Pd) unchanged material was obtained in high yield. A brown uncrystallisable oil was isolated on repeating the experiment at 95° in the presence of Adams' catalyst in acetic acid.

Due to the failure of direct hydrogenation it next appeared necessary to attempt to remove the benzyl group first and then to reduce the formyl by hydrogenation. Treatment of (CXIV) with concentrated hydrochloric acid in acetic acid removed the benzyloxy group, but, where it had been hoped to obtain methyl 4-benzoyloxy-3-formyl-2-hydroxy-6-methylbenzoate (CXVII), methyl haematomate (XCIII) was isolated. As a result of the apparent difficulties in synthesising (CXVI), further investigation of this route was abandoned.

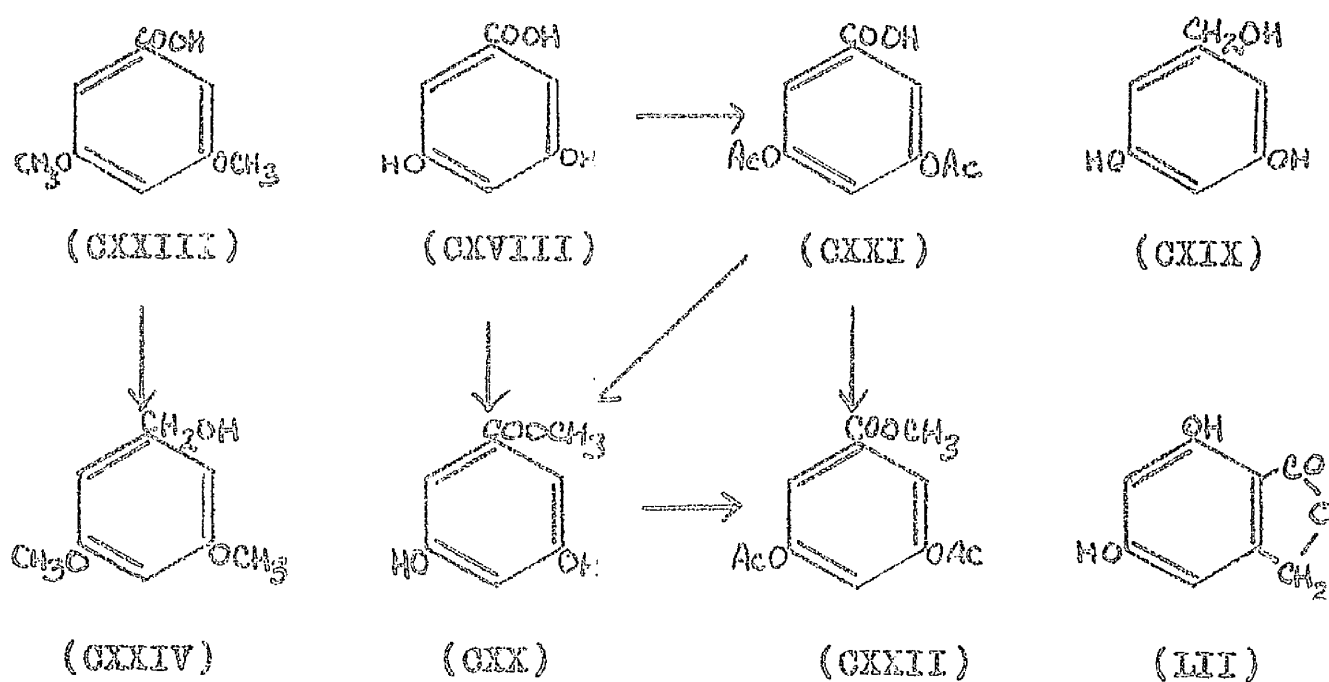
An alternative synthesis of (LXXX) from 3,5-dihydroxybenzoic acid<sup>59</sup> (CXVIII) was also explored. After reduction of (CXVIII) to 3,5-dihydroxybenzyl alcohol (CXIX) it was planned to introduce a carboxyl group, if possible, in the



position ortho to the hydroxymethyl group, thereby on lactonisation forming 5,7-dihydroxyphthalide (III). It was hoped to obtain the required product from this point by means of methylation of the 7-hydroxy group, formylation of the 6-position and reduction.

The reduction of 3,5-dihydroxybenzoic acid (CXVIII) by use of lithium aluminium hydride in tetrahydrofuran was attempted unsuccessfully. It was considered that the failure of the reaction might be due to precipitation of the lithium salt formed as an intermediate in the reaction. The reaction also failed, however, on using a large volume of tetrahydrofuran as solvent.

Although previous lack of success had been reported,<sup>60</sup> the reaction was repeated in ether. Again unreacted 3,5-dihydroxybenzoic acid (CXVIII) was returned in high yield.



Attempted reduction of methyl 3,5-dihydroxybenzoate (CXX), prepared as described in the literature,<sup>61</sup> using lithium aluminium hydride was unsuccessful also, (CXX) being returned unchanged.

Since it has been suggested<sup>60</sup> that in (CXVIII) the hydroxyl groups lessen the susceptibility of the carboxyl group towards reduction, all further work was carried out with compounds in which the hydroxyl groups were blocked. This was done, in the first instance, with easily removable acetyl groups.

3,5-Diacetoxybenzoic acid (CXXI), prepared by the literature method,<sup>62</sup> was refluxed with lithium aluminium hydride in ether. The acetyl groups were removed but no reduction took place, a high yield of 3,5-dihydroxybenzoic acid (CXVIII) being obtained.

Methyl 3,5-diacetoxybenzoate (CXXII) was prepared, as described in the literature,<sup>63</sup> by the action of acetic anhydride and concentrated sulphuric acid on methyl 3,5-dihydroxybenzoate (CXX) and was also obtained by the action of diazomethane on 3,5-diacetoxybenzoic acid (CXXI). The action of methanol and concentrated sulphuric acid on (CXXI) under Fischer-Speier conditions, however, yielded methyl 3,5-dihydroxybenzoate (CXX). Methyl 3,5-diacetoxybenzoate (CXXII) could not be reduced with lithium aluminium

hydride under the reaction conditions previously used; methyl 3,5-dihydroxybenzoate (CXX) was isolated. It appears in the latter two cases that removal of the acetyl group may have taken place initially, in which case no advantage would be obtained over (CXVIII) and (CXX).

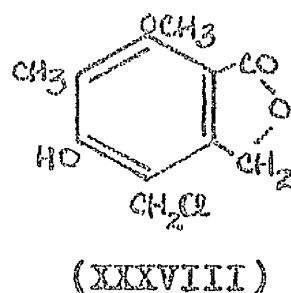
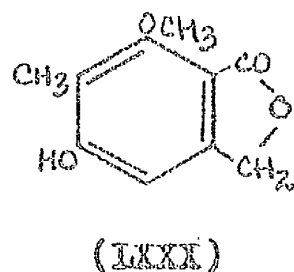
Despite the fact that the free hydroxyl groups would not be so readily recoverable, it became necessary at this point to attempt to reduce (CXVIII) in the form of its dimethyl ether, 3,5-dimethoxybenzoic acid (CXXIII). The latter compound, prepared by the literature method<sup>64</sup> in good yield using dimethyl sulphate and alkali, yielded 3,5-dimethoxybenzyl alcohol (CXXIV),<sup>65</sup> also in good yield. However, attempted demethylation by the action of hydrobromic acid and acetic acid<sup>66</sup> on (CXXIV) yielded a brown tar, while a similar reaction utilising anhydrous aluminium bromide<sup>66</sup> also failed to yield a crystalline product.

In the hope that benzyl groups might be more readily removable at the appropriate stage, benzylation of 3,5-dihydroxybenzoic acid (CXVIII) was attempted. No reaction took place on refluxing (CXVIII) in acetone with benzyl chloride and potassium carbonate for 12 hr., the starting material being returned in high yield. The reaction was repeated in dioxan without success, (CXVIII) again being isolated in high yield.

Smith and Stephen have reported<sup>67</sup> the development of a method of reduction of carboxylic acid groups by the action of diborane in bis(methoxyethyl) ether, the diborane being generated in situ by the action of sodium borohydride on boron trifluoride etherate. However, an attempt to reduce the carboxylic acid group in 3,5-diacetoxybenzoic acid (CXXI) by this means proved unsuccessful.

Work on this route was discontinued at this point and the route outlined from ethyl  $\beta$ -orcinol carboxylate (LXXXIV) was utilised to obtain 5-hydroxy-7-methoxy-6-methylphthalide (LXXX).

From (LXXX) it is possible, as previously mentioned, that a synthesis of cyclopaldic acid (VIII) might be achieved by means of a scheme of reactions via 4-chloromethyl-5-hydroxy-7-methoxy-6-methylphthalide (XXXVIII), corresponding to either of those used by Newbold et al.<sup>27,28,29</sup> in the synthesis of gladiolic acid (X).



### Discussion of Infrared and Ultraviolet Spectral Data

As stated in the Introduction, Duncanson, Grove and Zealley<sup>48</sup> have, on the basis of their own work in the field set out limits between which the carbonyl stretching frequencies of hydrogen-bonded ester carbonyl and phthalide carbonyl groups should lie in the infrared region, and have compared these with the corresponding limiting values for the unhindered groups. In this way much valuable information with regard to the structures of compounds in this field may be obtained.

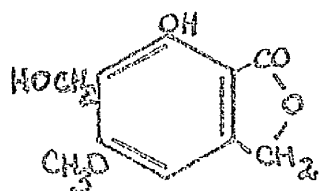
Examination of the carbonyl stretching frequencies of the compounds prepared in this work shows the values to be in agreement with the findings of these workers and with those of Grove and Willis.<sup>23</sup>

The infrared spectra of the phthalides prepared were obtained in the solid state as Nujol mulls, and in chloroform solution. The values are tabulated in the Appendix (Table I).

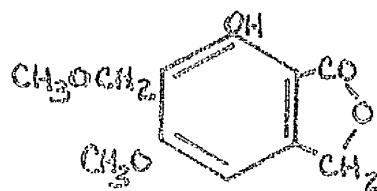
Intermolecular hydrogen-bonding occurs in the solid state with all phenolic phthalides and esters. Thus spectra determined from Nujol mulls do not reliably show the presence of intramolecular hydrogen-bonding between the ester or phthalide carbonyl and the ortho-hydroxyl group.

In solution intermolecular hydrogen-bonding breaks down and by examination of the spectra in this medium the depression of the carbonyl stretching frequency due to intramolecular hydrogen-bonding when present may be clearly seen.

From the data collected it was found that, with the exception of certain acetylated compounds, phthalides not possessing a free 7-hydroxyl group absorbed in the range 1751-1767  $\text{cm.}^{-1}$  in chloroform, while both the 7-hydroxy-phthalides prepared (LXXXVIII) and (XCI), gave values of 1736  $\text{cm.}^{-1}$ . Generally in the phthalide acetates, the acetate and phthalide carbonyl bands were unresolved and only a broad band was given. Successful resolution was, however, obtained in Nujol in each case.



(LXXXVIII)



(XCI)

As expected, the effect of intramolecular hydrogen-bonding was found to be even more marked in the case of the orthohydroxybenzoic acid esters when compared with the ortho-methoxybenzoic acid esters. The values of the carbonyl

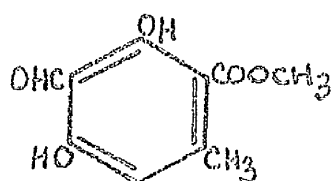
stretching frequencies of all such esters prepared in this work are set out in the Appendix (Table II).

The values determined for the orthomethoxybenzoic acid esters vary from 1721-1736  $\text{cm.}^{-1}$  in chloroform while those for the orthohydroxybenzoic acid esters lie in the range 1656-1672  $\text{cm.}^{-1}$ . As explained previously, the hydrogen-bonding in the 7-hydroxyphthalides is weaker than in the orthohydroxybenzoic acid esters since in the former the strain in the five-membered lactone ring pulls the phthalide carbonyl away from the 7-hydroxyl group.

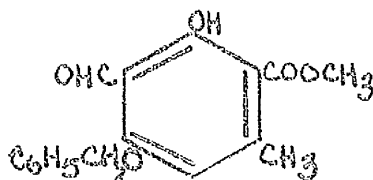
From the limits defined it is clear that unhindered phthalides are readily distinguishable from unhindered esters. However, hindered phthalides are not distinguishable from unhindered esters.

An interesting deviation from the anticipated spectra occurred in the case of the benzyl ethers (XCIV) and (XCV), prepared from methyl haematomate (XCIII). In methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate (XCIV) hydrogen bond formation might be expected between the ester carbonyl and the 2-hydroxyl group, and between the 3-formyl and the 2-hydroxyl group. However, if the absorption band at 1639  $\text{cm.}^{-1}$  in chloroform is assigned to the hydrogen-bonded aromatic aldehyde group, then the value of 1727  $\text{cm.}^{-1}$  for the frequency of the absorption band of the ester

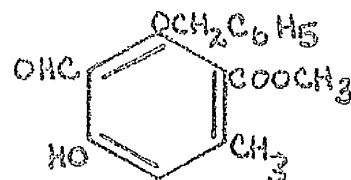
carbonyl indicates that it is not hydrogen-bonded.



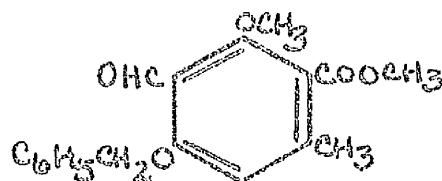
(XCIII)



(XCIV)



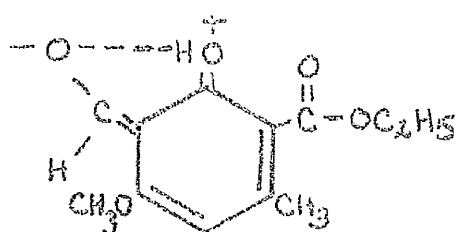
(XCV)



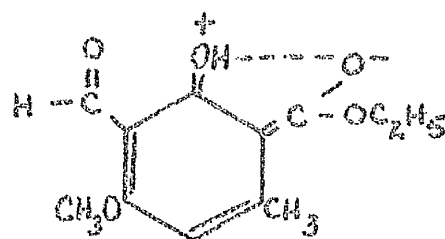
(XCVI)

Pauling<sup>68</sup> has pointed out that the C-O bond in phenols has some double bond character which will cause the hydrogen atom to lie in the plane of the ring. When a strong proton-accepting group is present in the ortho position two different configurations (CXXV) and (CXXVI) become possible. If it is agreed that the formyl group will be a stronger proton-accepting group than the ester group, then (CXXV) will be the more stable configuration and no hydrogen-bonding will take place between the 2-hydroxyl group and the ester carbonyl.





(CXXIV)



(CXXVI)

The correctness of the assignments made may be demonstrated by studying absorption frequencies of related compounds. In the case of methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (XCV) in chloroform, bands are found at 1727 and 1647  $\text{cm}^{-1}$ . If in methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate (XCIV) the 1639  $\text{cm}^{-1}$  band had been due to the hydrogen-bonded ester carbonyl, the value should have risen considerably in (XCV) due to the replacement of the 2-hydroxyl group. No appreciable rise did in fact take place. That the band at 1647  $\text{cm}^{-1}$  is due to the hydrogen-bonded aromatic aldehyde group is further demonstrated by the rise in frequency of absorption on conversion of (XCV) to (CXXVI) in which the aldehyde group could no longer be hydrogen-bonded.

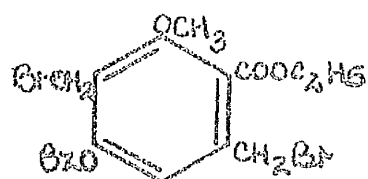
Further instances of unexpected values obtained from infrared spectra are to be found in certain acetylated and benzyloxy compounds prepared in this work.

Esters of aryl acids have been reported as absorbing between 1730 and 1717  $\text{cm.}^{-1}$  in chloroform,<sup>49</sup> depending on the degree and the nature of the ring substitution, while esters of saturated acids have been reported as absorbing in the range 1750-1735  $\text{cm.}^{-1}$ .

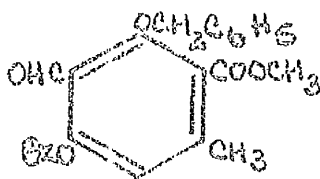
In this work, the band assignable to phenolic benzoate absorption has been found in esters in the range 1748-1757  $\text{cm.}^{-1}$  in chloroform. Similarly the band due to acetate absorption has been observed both in phthalides and in esters between 1770 and 1785  $\text{cm.}^{-1}$  in Nujol. Values in the same range have been reported by Allison and Newbold<sup>7</sup> for acetate absorption in the acetoxypthalides prepared in their work.

It would appear that the higher than normal frequencies of the acetoxy and benzyloxy groups in the 1700  $\text{cm.}^{-1}$  region must be due in this instance to the effect of the phenolic aromatic ring. A similar enhancement of frequency has been reported by Bellamy<sup>49</sup> in the case of vinyl esters and of phenyl acetate. The effect is shown also to become even more marked when electron-attracting groups are present on the phenolic aromatic ring. This latter point has been borne out also in this work by the greater enhancement of the absorption frequencies of (CXI) and of (CXIV) over

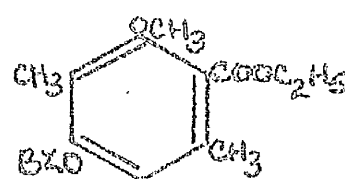
that of (CX), due to the influence of the ortho-bromomethyl and -formyl groups respectively.



(CXI)



(CXIV)



(CX)

On examination of the ultraviolet spectra of some orthomethoxy- and orthohydroxybenzoic acid esters and consideration of the maximum nearest the visible, Allison and Newbold<sup>7</sup> found that the introduction of a bromo-substituent into the side chain methyl group gave a series of bathochromic shifts ranging from 11 to 20 m $\mu$ , while substitution of bromine in the 3-position of the nucleus gave a smaller shift in the same direction. On consideration of the data in Tables I and II similar bathochromic shifts may be noted as shown:- (LXXI)  $\longrightarrow$  (LXXII)  $\Delta$  7, (LXXI)  $\longrightarrow$  (LXXIV)  $\Delta$  29, (LXXXVI)  $\longrightarrow$  (LXXXVII)  $\Delta$  11, (CII)  $\longrightarrow$  (CIII)  $\Delta$  28, (CX)  $\longrightarrow$  (CXI)  $\Delta$  2.

In the phthalides prepared in this work substitution of bromine in the nucleus was found also to bring about a bathochromic shift: (LXVI)  $\longrightarrow$  (LXXVI)  $\Delta$  17 and (LXXVIII)  $\longrightarrow$  (LXXVII)  $\Delta$  10.

## EXPERIMENTAL

All melting points are uncorrected. Ultraviolet absorption spectra were determined in ethanol and are tabulated, along with infrared data, in the Appendix. Ligroin refers to petroleum ether of boiling point 60-80° .

Methyl 3-Methoxy-4-methoxycarbonyl-5-methylphenyl Carbonate. - Methyl 3-hydroxy-4-methoxycarbonyl-5-methylphenyl carbonate<sup>53</sup> (3.5 g.) was dissolved in methanol (30 ml.) and treated with excess diazomethane in ether for 24 hr.

The solvent and the excess diazomethane was boiled off. The residue was dissolved in ether (100 ml.) and washed with sodium hydroxide (5%; 6 x 50 ml.). The alkali washings (300 ml.) were retained (see next experiment).

The ether solution was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to yield an oil which on trituration with ligroin gave a white solid material. Recrystallisation from the same solvent yielded methyl 3-methoxy-4-methoxycarbonyl-5-methylphenyl carbonate as needles (1.92 g.), m.p. and mixed m.p. 85-86° (lit.,<sup>53</sup> m.p. 85-86°). Specimens of the product and authentic methyl 3-methoxy-4-methoxycarbonyl-5-

methylphenyl carbonate had identical infrared spectra in Nujol.

Methyl 4-Hydroxy-6-methoxy-2-methylbenzoate. -

(a) Methyl 3-methoxy-4-methoxycarbonyl-5-methylphenyl carbonate (1.4 g.) was dissolved in methanol (11.2 ml.) and treated with 1N. aqueous sodium hydroxide (22.4 ml.) with shaking. The solution was allowed to stand for 2 hr. On acidification and standing crystalline material separated. Recrystallisation from ligroin-benzene gave methyl 4-hydroxy-6-methoxy-2-methylbenzoate (0.9 g.; 91%) as plates, m.p. 111-112° (Found: C, 60.9; H, 6.2.

$C_{10}H_{12}O_4$  requires C, 61.2; H, 6.2%).

(b) The alkaline washings from the methylation of methyl 3-hydroxy-4-methoxycarbonyl-5-methylphenyl carbonate were acidified and re-extracted with ether yielding, on removal of solvent, methyl 4-hydroxy-6-methoxy-2-methylbenzoate (0.75 g.) as plates, m.p. and mixed m.p. 111-112°. The preparations from (a) and (b) had identical infrared spectra in Nujol.

Methyl 3-Bromo-4-hydroxy-6-methoxy-2-methylbenzoate. -

Methyl 4-hydroxy-6-methoxy-2-methylbenzoate (0.177 g.), dissolved in dry carbon tetrachloride (30 ml.), was maintained under reflux and irradiated by a 150W. tungsten

lamp. Bromine (0.144 g.  $\approx$  1 mol.) in dry carbon tetrachloride (0.90 ml.) was added dropwise over 10 min.

Refluxing was continued for 20 min. Removal of the solvent under reduced pressure yielded a residue which on recrystallisation from ligroin gave methyl 3-bromo-4-hydroxy-6-methoxy-2-methylbenzoate (0.15 g.; 60%) as needles, m.p. 134-135° (Found: C, 43.8; H, 4.3.  $C_{10}H_{11}O_4Br$  requires C, 43.7; H, 4.0%).

Methyl 3-Bromo-4,6-dimethoxy-2-methylbenzoate. -

Methyl 3-bromo-4-hydroxy-6-methoxy-2-methylbenzoate (0.20 g.) was dissolved in methanol (30 ml.) and treated with excess ethereal diazomethane for 2 hr. Removal of solvent and recrystallisation from aqueous methanol gave methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate (0.19 g.) as needles, m.p. and mixed m.p. 120-121° (lit.,<sup>47</sup> m.p. 120-121°).

Specimens of the product and authentic methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate had identical infrared spectra in Nujol.

Methyl 3-Bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate. - Methyl 4-hydroxy-6-methoxy-2-methylbenzoate (1.3 g.), dissolved in dry carbon tetrachloride (30 ml.), was maintained under reflux and irradiated by a 150 W.

tungsten lamp. Bromine (2.12 g. = 2 mols.) in dry carbon tetrachloride (13.1 ml.) was added dropwise over 30 min. and refluxing was continued for a further 1 hr. The solvent was removed under reduced pressure. The residue crystallised from ligroin to give methyl 3-bromo-2-bromo-methyl-4-hydroxy-6-methoxybenzoate (1.48 g.; 62%) as prisms, m.p. 160-161° (Found: C, 34.3; H, 3.1; Br, 44.8.  $C_{10}H_{10}O_4Br_2$  requires C, 33.9; H, 2.8; Br, 45.1%).

Any appreciable cutting down of the ratio of carbon tetrachloride to solute affected the yield adversely.

4-Bromo-5-hydroxy-7-methoxyphthalide. - Methyl 3-bromo-2-bromomethyl-4-hydroxy-6-methoxybenzoate (0.95 g.) was dissolved in dioxan (30 ml.) and water (20 ml.) and heated under reflux for 44 hr. The solvent was removed under reduced pressure. White material separated and was recrystallised from chloroform-acetone to give 4-bromo-5-hydroxy-7-methoxyphthalide (0.63 g.; 89%) as an amorphous solid, m.p. 290° (decomp.) (Found: C, 42.0; H, 3.0; Br, 30.7.  $C_9H_7O_4Br$  requires C, 41.7; H, 2.7; Br, 30.8%).

The material was sparingly soluble in chloroform.

4-Bromo-5,7-dimethoxyphthalide. - 4-Bromo-5-hydroxy-7-methoxyphthalide (63 mg.) was dissolved in methanol



(10 ml.) and treated with excess diazomethane in ether for 4 hr. Removal of solvent yielded, on recrystallisation from ligroin, 4-bromo-5,7-dimethoxyphthalide (54 mg.) as felted needles, m.p. and mixed m.p. 246-248° (lit.,<sup>47</sup> m.p. 246-248°). Specimens of the product and authentic 4-bromo-5,7-dimethoxyphthalide had identical infrared spectra in Nujol.

5-Acetoxy-4-bromo-7-methoxyphthalide. - 4-Bromo-5-hydroxy-7-methoxyphthalide (0.14 g.) was dissolved in acetic anhydride (5 ml.) containing concentrated sulphuric acid (1 drop). The solution was heated on a steam bath for 2½ hr., poured into cold water and allowed to stand for 30 min. The precipitated solid was collected and recrystallised from ligroin-benzene to give 5-acetoxy-4-bromo-7-methoxyphthalide (0.12 g.; 74%) as plates, m.p. 142-143° (Found: C, 43.7; H, 3.4.  $C_{11}H_9O_5Br$  requires C, 43.9; H, 3.1%).

Attempted Hydrogenolysis of 4-Bromo-5-hydroxy-7-methoxyphthalide. - 4-Bromo-5-hydroxy-7-methoxyphthalide (0.1 g.) was dissolved in dry ethyl acetate (80 ml.) and shaken at room temperature and atmospheric pressure with hydrogen in the presence of palladised charcoal (2.5%  $PdCl_2$ ) (0.4 g.) and magnesium oxide (0.8 g.). After 15 hr. the mixture

was filtered and the insoluble material was extracted with boiling chloroform (3x100 ml.). The combined extracts and filtrate were evaporated and the residue on recrystallisation from acetone gave unchanged material (85 mg.) identified by its m.p., mixed m.p. and infrared spectrum.

The experiment was repeated for a range of reaction times up to 60 hr. using firstly palladised charcoal and magnesium oxide in the proportions detailed above, and secondly pre-reduced Adams' catalyst (0.2 g.) and magnesium oxide (0.4 g.). No debromination took place.

5-Acetoxy-7-methoxyphthalide. - 5-Acetoxy-4-bromo-7-methoxyphthalide (0.45 g.) was dissolved in dry ethyl acetate (35 ml.) and shaken with hydrogen for 40 hr. at room temperature and atmospheric pressure in the presence of pre-reduced Adams' catalyst (0.45 g.) and magnesium oxide (0.8 g.). Filtration and extraction of the residual solid with chloroform (3 x 50 ml.) yielded, on evaporation of the combined liquids, white amorphous solid which was recrystallised from ligroin-benzene to give 5-acetoxy-7-methoxyphthalide (0.27 g.; 81%) as stout needles, m.p. 161-162° (Found: C, 59.3; H, 4.9.  $C_{11}H_{10}O_5$  requires C, 59.5; H, 4.5%).

5-Hydroxy-7-methoxyphthalide. - 5-Acetoxy-7-methoxy-

phthalide (0.28 g.) was dissolved in 1N. potassium hydroxide (9 ml.) and heated on a steam bath for  $1\frac{1}{2}$  hr. The solution was cooled and acidified (Congo red), and the material which separated on further cooling was collected and recrystallised from methanol to give 5-hydroxy-7-methoxyphthalide (0.19 g.; 82%) as prisms, m.p. 280-283° (decomp., in a sealed tube) (Found: C, 60.1; H, 4.8.  $C_9H_8O_4$  requires C, 60.0; H, 4.5%).

5,7-Dimethoxyphthalide. - 5-Hydroxy-7-methoxyphthalide (65 mg.) was dissolved in methanol (20 ml.) and treated with excess ethereal diazomethane over a period of 2 hr. The solvent and remaining diazomethane was removed by evaporation and the residual solid on recrystallisation from chloroform-ligroin yielded 5,7-dimethoxyphthalide (50 mg.) as needles, m.p. and mixed m.p. 151-153° (lit.,<sup>47</sup> m.p. 151-153°). The specimens of the product and authentic 5,7-dimethoxyphthalide had identical infrared spectra in Nujol.

Ethyl 2,4-Dihydroxy-3-dimethylaminomethyl-6-methylbenzoate. - Ethyl 2,4-dihydroxy-6-methylbenzoate (ethyl orsellinate)<sup>52</sup> (5 g.) was refluxed with bis(dimethylamino)-methane (2.85 g.) in methanol (225 ml.) for  $1\frac{1}{4}$  hr. under nitrogen. The solvent was removed under reduced pressure

to yield a brown oil which on recrystallisation from methanol gave ethyl 2,4-dihydroxy-3-dimethylaminomethyl-6-methylbenzoate (3.81 g.; 59%) as prisms, m.p. 80-81° (Found: C, 61.9; H, 7.6; N, 5.7.  $C_{15}H_{19}O_4N$  requires C, 61.6; H, 7.6; N, 5.5%).

Ethyl 2,4-Dihydroxy-3,6-dimethylbenzoate (Ethyl  $\beta$ -Orcinol Carboxylate). - (a) Ethyl 2,4-dihydroxy-3-dimethylaminomethyl-6-methylbenzoate (2.1 g.) was dissolved in acetic acid (50 ml.) and shaken in an atmosphere of hydrogen at atmospheric pressure and a temperature of 95° in the presence of palladised charcoal (10% Pd) (70 mg.) for 18 hr. The catalyst was removed by filtration and washed with acetic acid (3 x 50 ml.). The combined solution was concentrated under reduced pressure, and on the addition of water (150 ml.) a white solid was obtained which, on filtration and recrystallisation from ligroin-benzene, gave ethyl  $\beta$ -orcinol carboxylate (1.53 g.; 87%) as plates, m.p. and mixed m.p. 127-128° (lit.,<sup>55</sup> m.p. 127-128°). The product and an authentic sample of ethyl  $\beta$ -orcinol carboxylate showed identical infrared spectra in Nujol.

On shaking the amine (2.1 g.) in glacial acetic acid (70 ml.) for 25 hr. under otherwise identical conditions, ethyl  $\beta$ -orcinol carboxylate (0.69 g.) was obtained as plates,

m.p. and mixed m.p. 127-128°. The aqueous mother liquors (150 ml.) were extracted with ether (5 x 30 ml.) and the ethereal solution was washed with sodium bicarbonate (4 x 20 ml.) and with water until neutral. Drying and evaporation of the solvent yielded a brown oil which on fractional distillation in vacuo gave as the main fraction (0.82 g.) a colourless oil, b.p. 87-88°/2 mm. The oil was redistilled until a constant refractive index was obtained,  $n_D^{18}$  1.4570 (Found: C, 66.7; H, 9.5%).

(b) Ethyl haematomate<sup>54</sup> (0.3 g.) in ethanol (20 ml.) was added over a period of 30 min. to a gently boiling solution of hydrochloric acid (9 ml., 6 ml. concentrated hydrochloric acid and 3 ml. water) containing zinc amalgam (1.5 g.). The mixture was refluxed for a further 4½ hr., after which the aqueous solution was decanted and the zinc residue washed with hot ethanol (3 x 20 ml.). Concentration of the combined solution and cooling yielded brown crystalline material which on recrystallisation from ligroin-benzene gave ethyl  $\beta$ -orcinol carboxylate (85 mg.; 30%) as plates, m.p. and mixed m.p. 127-128°. The products from preparations (a) and (b) had identical infrared spectra in Nujol. The mother liquors were diluted with water (100 ml.) and extracted with ether (3 x 30 ml.). The

etheral solution was washed with saturated sodium bicarbonate (3 x 20 ml.) and with water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation yielded a yellow solid which on recrystallisation from ethanol gave yellow needles (100 mg.), which were confirmed to be unchanged ethyl haematommate by comparison of infrared spectra in Nujol.

(c) Ethyl haematommate (1 g.) was added to a mixture of amalgamated zinc (2.5 g.), concentrated hydrochloric acid (7 ml.), water (3 ml.) and toluene (10 ml.). The mixture was refluxed on a mantle for 40 hr. Portions of concentrated hydrochloric acid (2 ml.) were added at 12 hr. intervals. The phases were separated by decantation and the aqueous phase was diluted by water (100 ml.) and extracted with ether (3 x 50 ml.). The combined organic solutions were washed with saturated sodium bicarbonate (3 x 50 ml.) and with water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation yielded a brown gum which on recrystallisation from ethanol gave ethyl haematommate (0.62 g.) unchanged, again confirmed by comparison of infrared spectra in Nujol.

The recrystallisation mother liquors were bulked and concentrated. On repeated recrystallisation of the brown solid which separated, ethyl  $\beta$ -orcinol carboxylate

(0.23 g.; 25%) was obtained as plates, m.p. and mixed m.p. 127-128°. The infrared spectrum of the product in Nujol was identical with that of authentic material.

(d) Ethyl haematomate (2.23 g.), dissolved in glacial acetic acid (70 ml.), was shaken at room temperature and atmospheric pressure in an atmosphere of hydrogen in the presence of pre-reduced Adams' catalyst (1.52 g.).

After uptake of the theoretical amount of hydrogen (450 ml.) the solvent was reduced to small bulk and a few ml. of water were added. The solid which separated, recrystallised from ligroin-benzene to yield ethyl  $\beta$ -orcinol carboxylate (1.52 g.; 73%) as needles, m.p. and mixed m.p. 127-128°.

Confirmation of the identity of the product was obtained by comparison of infrared spectra.

Ethyl 3,6-Dimethyl-2-hydroxy-4-methoxybenzoate (Ethyl Rhizonate).<sup>55</sup> - Ethyl  $\beta$ -orcinol carboxylate (1 g.), dissolved in methanol (20 ml.), was treated with excess diazomethane in ether for 3 hr. The ether and excess diazomethane was partially evaporated, whereupon ethyl 3,6-dimethyl-2-hydroxy-4-methoxybenzoate (0.8 g.; 75%) separated as long needles, m.p. and mixed m.p. 80-81° (lit.,<sup>55</sup> m.p. 80-81°). Specimens of the product and

authentic ethyl 3,6-dimethyl-2-hydroxy-4-methoxybenzoate had identical infrared spectra in Nujol.

It was essential to keep the quantity of methanol used to a minimum to ensure maximum yields.

Ethyl 3,6-Di(bromomethyl)-2-hydroxy-4-methoxybenzoate. -

Ethyl rhizonate (0.9 g.) was dissolved in dry carbon tetrachloride (30 ml.) in a quartz flask, heated and irradiated by a 150 W. lamp. Bromine (1.30 g. ~~was~~ 2 mols.), dissolved in carbon tetrachloride (8.0 ml.), was added dropwise to the refluxing solution over a period of 20 min. and refluxing was continued for 30 min. On removal of solvent under reduced pressure a brown solid was obtained which on recrystallisation from ligroin-benzene gave ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (0.84 g.; 54%) as needles, m.p. 167-168° (Found: C, 38.2; H, 3.7; Br, 41.4.  $C_{12}H_{14}O_4Br_2$  requires C, 37.8; H, 3.7; Br, 41.8%).

7-Hydroxy-6-hydroxymethyl-5-methoxyphthalide. - Ethyl

3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (1.0 g.) was dissolved in dioxan (120 ml.) and water (30 ml.) and refluxed on a mantle for 30 hr. The solvent mixture was removed under reduced pressure until a white gummy solid separated. Repeated recrystallisation from chloroform



yielded 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (0.11 g.; 20%) as white felted needles, m.p. 217-220° (decomp.) (Found: C, 56.7; H, 4.8.  $C_{10}H_{10}O_5$  requires C, 57.1; H, 4.8%).

Further evaporation of the reaction mixture yielded a brown gum which on infrared spectral examination was found to contain an absorption band in the carbonyl region identical with that of the crystalline product.

The oil was re-treated by the experimental procedure as described above. No crystalline product was obtained.

In a repeat experiment the aqueous dioxan solution of ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (1.0 g.) was refluxed for 6 hr. The product was obtained in 22% yield.

(b) Ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (0.28 g.) was refluxed in acetone (40 ml.) and water (25 ml.) for 20 hr. White material separated on partial removal of solvent. Recrystallisation from chloroform gave 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (58 mg.; 38%) as felted needles, m.p. and mixed m.p. 217-220° (decomp.). The infrared spectrum of the product in Nujol was identical with that of the product in experiment (a).

(c) 7-Acetoxy-6-acetoxymethyl-5-methoxyphthalide (0.1 g.) was dissolved in 1N. sodium hydroxide (10 ml.) and heated

on a steam bath for  $1\frac{1}{2}$  hr. The solution was diluted with water, acidified (Congo red) and extracted with ether (4 x 50 ml.). The ethereal solution was washed with saturated sodium bicarbonate solution (3 x 30 ml.) and with water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation yielded white solid which on recrystallisation from chloroform gave 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (50 mg.; 70%) as felted needles, m.p. and mixed m.p.  $217-220^\circ$  (decomp.). The infrared spectrum of the product in Nujol was identical with those from preparations (a) and (b).

7-Acetoxy-6-acetoxymethyl-5-methoxyphthalide. -

(a) Ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (0.25 g.) was dissolved in acetic anhydride (30 ml.) and refluxed for  $3\frac{1}{2}$  hr. The solution was poured into water and extracted with ether (4 x 50 ml.). The ethereal solution was washed with saturated sodium bicarbonate solution (4 x 30 ml.) and with water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation of solvent under reduced pressure yielded a colourless gum which on recrystallisation from chloroform-ligroin gave 7-acetoxy-6-acetoxymethyl-5-methoxyphthalide (78 mg.; 40%) as needles, m.p.  $148-150^\circ$  (Found: C, 57.3; H, 5.2.  $\text{C}_{14}\text{H}_{14}\text{O}_7$  requires C, 57.1; H, 4.8%).

(b) 7-Hydroxy-6-hydroxymethyl-5-methoxyphthalide (70 mg.) was dissolved in acetic anhydride (5 ml.) and concentrated sulphuric acid (1 drop) was added. The solution was heated on a steam-bath for  $2\frac{1}{2}$  hr. and poured into a large excess of water. Ether extraction (4 x 30 ml.) in the normal manner yielded, on evaporation of solvent, white amorphous material which on recrystallisation from chloroform gave 7-acetoxy-6-acetoxymethyl-5-methoxyphthalide (82 mg.; 83%) as felted needles, m.p. and mixed m.p. 148-150°.

The products of (a) and (b) had identical infrared spectra in Nujol.

7-Hydroxy-5-methoxy-6-methoxymethylphthalide. - Ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (0.4 g.) was dissolved in methanol (200 ml.) and water (50 ml.) and refluxed for 12 hr. The solvent was completely removed by evaporation and the brown residue was recrystallised from chloroform-methanol to yield 7-hydroxy-5-methoxy-6-methoxymethylphthalide (0.12 g.; 51%) as needles, m.p. (in vacuo) 235° (decomp.) (Found: C, 58.9; H, 5.3; OMe, 27.3.  $C_{11}H_{12}O_5$  requires C, 58.9; H, 5.4; OMe, 27.7%).

The residual brown oil obtained on evaporation of the mother liquors could not be purified.

Attempted Preparation of 7-Hydroxy-5-methoxy-6-methylphthalide. - 7-Hydroxy-6-hydroxymethyl-5-methoxyphthalide (0.15 g.) was dissolved in ethyl acetate (40 ml.) and shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure in the presence of pre-reduced Adams' catalyst (0.12 g.) for 20 hr. The catalyst was filtered off and thoroughly washed with fresh ethyl acetate. The filtrate and washings were evaporated under reduced pressure to yield a white solid which on recrystallisation from chloroform gave unchanged 7-hydroxy-6-hydroxymethyl-5-methoxyphthalide (0.14 g.), confirmed by m.p. and mixed m.p. determinations and comparison of infrared spectra.

Methyl 4-Benzoyloxy-3-formyl-2-hydroxy-6-methylbenzoate. - Methyl haematomate<sup>54</sup> (1.0 g.) was dissolved in acetone (30 ml.) and treated with benzyl chloride (1.1 g.), potassium carbonate (0.35 g.) and sodium iodide (0.70 g.). The mixture was refluxed for 6 hr. and the solvent was removed by evaporation under reduced pressure. The soluble portion of the residual material was taken up in ether and the insoluble material, after collection by filtration, was thoroughly washed with ether (3 x 50 ml.). The ethereal solutions were combined, washed once with

saturated sodium bicarbonate (50 ml.) and shaken with 1N. sodium hydroxide (15 ml.) until a yellow precipitate separated. The organic solution was shaken with further volumes (15 ml.) of 1N. sodium hydroxide until no further yellow precipitate was formed. The precipitate so formed was removed by filtration and was dissolved in water. The aqueous solution was acidified and extracted with ether to yield on evaporation of the water-washed ethereal solution a brown gum (0.55 g.) which recrystallised from ethanol to give methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate (0.35 g.; 25%) as needles, m.p. 89-90° (lit.,<sup>58</sup> m.p. 91°).

Methyl 2-Benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate. - The residual ether solution from the previous experiment was extracted with further volumes of 1N. sodium hydroxide (2 x 50 ml.) which were combined with the filtrates of the alkaline extracts previously obtained. Acidification and ether extraction yielded a yellow gum (0.80 g.) which on recrystallisation from ethanol gave methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (0.55 g.; 39%) as plates, m.p. 110-112° (lit.,<sup>58</sup> m.p. 112.5°).

Methyl 4-Benzoyloxy-3-formyl-2-methoxy-6-methyl-  
benzoate. - Methyl 4-benzyloxy-3-formyl-2-hydroxy-6-  
 methylbenzoate (1 g.) was dissolved in acetone (100 ml.)  
 and treated with methyl iodide (1 ml.) and potassium  
 carbonate (1.14 g.). The mixture was refluxed for 8 hr.  
 and the solvent was removed by evaporation under reduced  
 pressure. Ether was added and the insoluble residue was  
 filtered off and washed with ether (3 x 50 ml.). The  
 combined ethereal solutions were washed with 1N. sodium  
 hydroxide (2 x 30 ml.) and with water (3 x 20 ml.).  
 Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation yielded a colourless gum  
 (0.98 g.) which was recrystallised from ethanol to give  
 methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate  
 (0.64 g.; 61%) as prisms, m.p. and mixed m.p. 80-81°  
 (lit.,<sup>58</sup> m.p. 80°).

Methyl 3,6-Dimethyl-4-hydroxy-2-methoxybenzoate  
(Methyl Isorhizonate). - (a) Methyl 4-benzyloxy-3-formyl-  
 2-methoxy-6-methylbenzoate (0.1 g.) was dissolved in  
 glacial acetic acid (20 ml.) and shaken in an atmosphere of  
 hydrogen at atmospheric pressure and a temperature of 95°  
 in the presence of palladised charcoal (10% Pd) (90 mg.) for  
 6 hr. The catalyst was removed by filtration and  
 thoroughly washed with glacial acetic acid. The combined  
 acetic acid solutions were concentrated to small volume

(c. 5 ml.). Water (100 ml.) was added and the solution was extracted with ether (3 x 20 ml.). The ethereal solution (solution A) was washed with saturated sodium bicarbonate (3 x 10 ml.) and shaken with 1N. sodium hydroxide (3 x 20 ml.). The alkaline solution was acidified and extracted with ether (3 x 20 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 10 ml.) and with water until neutral. No product was obtained on evaporation of the dried ethereal solution.

Solution A was washed with water until neutral. Drying and evaporation yielded a gum which partially crystallised from ethanol to yield unchanged material (59 mg.), m.p. 80°. The product and starting material had identical infrared spectra in Nujol.

(b) Methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (0.1 g.) was dissolved in glacial acetic acid (35 ml.) and shaken with hydrogen at atmospheric pressure and a temperature of 95° for 20 hr. in the presence of palladised charcoal (10% Pd) (90 mg.). By use of the experimental procedure detailed in (a) a brown gum (28 mg.) was obtained from the NaOH extract. This crystallised from ligroin to give methyl isorhizonate (10 mg.; 15%) as small needles, m.p. 141-142° (lit.,<sup>58</sup> m.p. 143°). The original ethereal solution yielded an uncrystallisable gum (60 mg.).

(c) Methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (0.1 g.) was dissolved in glacial acetic acid (30 ml.) and shaken with hydrogen at atmospheric pressure and a temperature of 95° in the presence of palladised charcoal (20% Pd) (90 mg.) for 40 hr. The subsequent experimental procedure was carried out as in (a). A gum (30 mg.) was obtained from the NaOH extract. This crystallised from cyclohexane to give methyl isorhizonate (18 mg., 27%) as needles, m.p. and mixed m.p. 141-142°. The original ethereal solution yielded an uncrystallisable gum (55 mg.).

(d) Methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (0.1 g.) was dissolved in glacial acetic acid (30 ml.) and shaken with hydrogen at atmospheric pressure and a temperature of 95° for 40 hr. in the presence of pre-reduced Adams' catalyst (90 mg.). Employing the experimental procedure described in (a) a brown gum (20 mg.) was isolated from the NaOH extract, which crystallised to some extent from cyclohexane to give methyl isorhizonate (10 mg.; 15%), m.p. and mixed m.p. 141-142°.

An uncrystallisable gum (65 mg.) was isolated from the original ether solution.

(e) Methyl 3-formyl-4-hydroxy-2-methoxy-6-methylbenzoate



(0.11 g.) was dissolved in glacial acetic acid (25 ml.) and shaken for 30 hr. at atmospheric pressure and a temperature of 95° with hydrogen in the presence of palladised charcoal (10% Pd) (0.1 g.). The catalyst was removed by filtration and washed with glacial acetic acid. The filtrate was concentrated, diluted with water (100 ml.) and extracted with ether (3 x 25 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 15 ml.) and with water until neutral. Evaporation of the dried solution yielded a white solid (75 mg.) which on recrystallisation from chloroform-ligroin gave methyl isorhizonate (70 mg.; 71%) as needles, m.p. and mixed m.p. 142-143°.

The infrared spectra in Nujol of the acidic products from preparations (b), (c), (d) and the main product from (e) were identical with one another.

Methylation of Methyl 2,4-Dihydroxy-3-formyl-6-methylbenzoate (Methyl Haematommate). - Methyl haematommate (3 g.) was dissolved in acetone (30 ml.) and refluxed in the presence of methyl iodide (10 ml.), potassium carbonate (1.05 g.) and sodium iodide (2.1 g.) for 24 hr. The solvent was removed and the organic residue was dissolved in ether (250 ml.). The inorganic material was removed by filtration and washed with ether (3 x 40 ml.). The

combined ethereal solutions were extracted with 1N. sodium hydroxide (4 x 30 ml.). Acidification of the alkaline solution and ether extraction yielded a brown gum, which on recrystallisation from methanol gave unchanged methyl haematommate (0.97 g.). The mother liquors were further concentrated and the solvent was completely removed to yield a brown gum. The gum crystallised from cyclohexane and, after repeated recrystallisation from this solvent, was separated into two compounds, (1) methyl 3-formyl-4-hydroxy-2-methoxy-6-methylbenzoate (0.41 g.; 13%) obtained as felted needles, m.p. and mixed m.p. 63-64° (lit.,<sup>58</sup> m.p. 64°), and (2) methyl 3-formyl-2-hydroxy-4-methoxy-6-methylbenzoate (0.81 g.; 25%) obtained as needles, m.p. and mixed m.p. 86-87° (lit.,<sup>53</sup> m.p. 87°).

The products had identical infrared spectra in Nujol with the authentic specimens of the respective compounds.

Methyl 3-Formyl-4-hydroxy-2-methoxy-6-methylbenzoate. - Methyl 4-benzyloxy-3-formyl-2-methoxy-6-methylbenzoate (1.64 g.) was dissolved in glacial acetic acid (140 ml.) and treated with concentrated hydrochloric acid (60 ml.), saturated at 0° with hydrogen chloride gas. The solution was heated on a steam-bath for 30 min. and then boiled in an oil-bath for 1 min. The acid solution was evaporated

to dryness. The residue was suspended in water and was extracted by ether (4 x 50 ml.). The ethereal solution was washed with saturated sodium bicarbonate (2 x 25 ml.) and was thoroughly shaken with 1N. sodium hydroxide (4 x 50 ml.). The alkaline solution was acidified with dilute hydrochloric acid and was extracted in the normal manner with ether, removal of which under reduced pressure yielded a colourless gum (1.05 g.). Recrystallisation from cyclohexane gave methyl 3-formyl-4-hydroxy-2-methoxy-6-methylbenzoate (0.66 g.; 57%) as prisms, m.p. 63°, identified by mixed m.p. determination and infrared comparison.

Ethyl 2,5-Dimethyl-4-ethoxycarbonyl-3-hydroxyphenyl Carbonate. - Ethyl 2,4-dihydroxy-3,6-dimethylbenzoate (ethyl  $\beta$ -orcinol carboxylate) (5.9 g.) was dissolved in 1N. sodium hydroxide (28 ml.) and ethyl chloroformate (4.9 g.) was added. The mixture was shaken for 8 min. and allowed to stand for 1 hr. The separated material was filtered off and recrystallised twice from ethanol to give ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-hydroxyphenyl carbonate (5.27 g.; 67%) as needles, m.p. 74-75° (Found: C, 59.9; H, 6.7.  $C_{14}H_{18}O_6$  requires C, 59.6; H, 6.4%).

Ethyl 2,5-Dimethyl-4-ethoxycarbonyl-3-methoxyphenyl Carbonate. - Ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-

hydroxyphenyl carbonate (3.27 g.) was dissolved in ethanol (100 ml.) and treated with excess diazomethane for 24 hr. The solvent and excess diazomethane was evaporated off cautiously. The oil so obtained was re-dissolved in ether (150 ml.) and the solution was washed with 1N. sodium hydroxide (4 x 25 ml.) and then with water until neutral. Drying and evaporation of the solvent yielded ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-methoxyphenyl carbonate (3.30 g.; 96%) as a pale yellow oil, b.p. 81-82°/0.5 mm. (Found: C, 60.7; H, 7.1.  $C_{15}H_{20}O_6$  requires C, 60.8; H, 6.8%).

Ethyl 3,6-Dimethyl-4-hydroxy-2-methoxybenzoate  
(Ethyl Isorhizonate). - The oil (3.30 g.) from the previous experiment, dissolved in ethanol (55 ml.), was treated with 1N. sodium hydroxide (40 ml.). The solution was allowed to stand for 2 hr. and then acidified. The product was extracted with ether (3 x 50 ml.) and the ethereal solution was shaken with 1N. sodium hydroxide (6 x 40 ml.). The alkaline solution was acidified and shaken with ether, which yielded on evaporation ethyl isorhizonate (2.04 g.; 81%) as plates from cyclohexane, m.p. 101-103° (Lit.,<sup>57</sup> m.p. 103°).

3,6-Dimethyl-4-hydroxy-2-methoxybenzoic Acid  
(Isorhizonic Acid). - (a) Methyl isorhizonate (90 mg.)

was treated with concentrated sulphuric acid (0.3 g.) and the solution was allowed to stand for 5 hr. Ice and water were added and the product was extracted with ether (5 x 30 ml.). The ethereal solution was shaken with saturated sodium bicarbonate (4 x 30 ml.). The alkaline solution was acidified and ether extraction, in the normal manner, yielded a brown solid which on recrystallisation from benzene gave isorhizonic acid as needles, m.p. 151-153° (lit.,<sup>57</sup> m.p. 155-157°).

(b) Ethyl isorhizonate (90 mg.) was treated with concentrated sulphuric acid (0.4 g.) and the solution was allowed to stand for 6 hr. The reaction was destroyed by the addition of ice and the product, isorhizonic acid, was isolated as in the previous experiment as felted needles, m.p. and mixed m.p. 152-153°. The infrared spectra of preparations (a) and (b) in Nujol were identical.

Ethyl 3,6-Di(bromomethyl)-4-hydroxy-2-methoxybenzoate. -

Ethyl 3,6-dimethyl-4-hydroxy-2-methoxybenzoate (1.6 g.), dissolved in dry carbon tetrachloride (320 ml.), was refluxed and irradiated by a 150 W. lamp. Bromine (2.24 g.  $\equiv$  2 mols.) in dry carbon tetrachloride (14.1 ml.) was added dropwise over a period of 1½ hr.

The solvent was removed under reduced pressure and the

residual oil was crystallised from a dry benzene-ligroin mixture to yield ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (1.12 g.; 41%) as prisms, m.p. (in vacuo) 110-112° (decomp.) (Found: C, 38.7; H, 4.0; Br, 39.2; C, 39.0; H, 4.1; Br, 39.6.  $C_{12}H_{14}O_4Br_2$  requires C, 37.7; H, 3.7; Br, 41.8%).

Any appreciable cutting down in the ratio of carbon tetrachloride to solute affected the yield adversely.

5-Hydroxy-6-hydroxymethyl-7-methoxyphthalide. -

(a) Ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (0.43 g.) was refluxed with acetone (50 ml.) and water (30 ml.) for  $5\frac{1}{2}$  hr. The solution was partially evaporated and a white solid separated which on recrystallisation from acetone-benzene gave 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (0.16 g.; 68%) as felted needles, m.p. 320° (decomp.) (Found: C, 57.4; H, 5.2.  $C_{10}H_{10}O_5$  requires C, 57.1; H, 4.8%).

(b) 5-Acetoxy-6-acetoxymethyl-7-methoxyphthalide (80 mg.) was dissolved in 1N. sodium hydroxide (10 ml.) and heated on a steam-bath for 2 hr. The solution was diluted with water (100 ml.), acidified (Congo red) and extracted with ether (3 x 40 ml.). The ethereal solution was washed with saturated sodium bicarbonate solution (3 x 20 ml.) and with

water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation yielded white crystals which on recrystallisation from acetone-benzene gave 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (40 mg.; 70%) as felted needles, m.p. (in vacuo)  $320^\circ$  (decomp.).

(c) Ethyl 4-benzoyloxy-3,6-di(bromomethyl)-2-methoxybenzoate (0.25 g.) was dissolved in dioxan (50 ml.) and water (13 ml.), and the solution was refluxed on a mantle for 22 hr. A large proportion of the solvent was removed under reduced pressure and on cooling a white solid separated, which on recrystallisation from acetone-benzene yielded 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (46 mg.; 43%) as felted needles, m.p. (in vacuo)  $320^\circ$  (decomp.) (Found: C, 56.9; H, 5.1. Calc. for  $\text{C}_{10}\text{H}_{10}\text{O}_5$ : C, 57.1; H, 4.8%).

The aqueous mother liquors were diluted with water (100 ml.) and made alkaline with 1N. sodium hydroxide (10 ml.). The alkaline solution was washed with ether (3 x 20 ml.) and then acidified. The acid solution was extracted with ether (3 x 20 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 10 ml.) and with water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation of solvent yielded a colourless oil which

crystallised from methanol to give 5-benzoyloxy-6-hydroxy-methyl-7-methoxyphthalide (18 mg.; 11%) as needles, m.p. 145-147° (Found: C, 65.2; H, 4.1.  $C_{17}H_{14}O_6$  requires C, 65.0; H, 4.5%).

(d) 5-Benzoyloxy-6-hydroxymethyl-7-methoxyphthalide (40 mg.), dissolved in 1N. sodium hydroxide (6 ml.), was heated on a steam-bath for  $2\frac{1}{2}$  hr. The solution was diluted with water (100 ml.), acidified (Congo red) and extracted with ether (3 x 30 ml.). The ethereal solution was washed with saturated sodium bicarbonate solution (3 x 20 ml.) and with water until neutral. Drying ( $Na_2SO_4$ ) and evaporation yielded solid material which was recrystallised from acetone-benzene to yield 5-hydroxy-6-hydroxymethyl-7-methoxyphthalide (22 mg.; 80%) as felted needles, m.p. (in vacuo) 320° (decomp.).

The sole products from preparations (a), (b) and (d) and the major product from preparation (c) had identical infrared spectra in Nujol and gave no depression on mixed m.p. determination in vacuo.

Attempted Preparation of 5-Hydroxy-6-hydroxymethyl-7-methoxyphthalide. - (a) Ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (0.22 g.) was dissolved in dioxan (50 ml.) and water (12 ml.) and refluxed for 20 hr. On partial evaporation of the solvent an amorphous material



(90 mg.), insoluble in organic solvents, separated. On dissolving the material in alkali, and acidifying the solution the same amorphous material insoluble in organic solvents, was reprecipitated, m.p.  $>300^{\circ}$ .

(b) Ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (0.2 g.), dissolved in dioxan (20 ml.) and water (5 ml.), was refluxed for 6 hr. On partial removal of the solvent no solid material was obtained. The concentrated reaction solution was diluted by water and extracted with ether (3 x 50 ml.) in the normal manner. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation gave a brown oil (0.12 g.) which could not be crystallised.

5-Hydroxy-7-methoxy-6-methoxymethylphthalide. - Ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (0.7 g.) was refluxed in methanol (70 ml.) and water (40 ml.) for  $8\frac{1}{2}$  hr. on a mantle. The solution was concentrated to small bulk under reduced pressure and a white solid separated, which was recrystallised from methanol to yield 5-hydroxy-7-methoxy-6-methoxymethylphthalide. (0.28 g.; 68%) as needles, m.p. (in vacuo)  $285^{\circ}$  (decomp.) (Found: C, 59.0; H, 5.8; OMe, 27.3.  $\text{C}_{11}\text{H}_{12}\text{O}_5$  requires C, 58.9; H, 5.4; OMe, 27.7%).

5-Acetoxy-6-acetoxymethyl-7-methoxyphthalide. -

(a) Ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (0.36 g.) was dissolved in acetic anhydride (30 ml.) and was refluxed for 3 hr. The reaction mixture was poured into water and heated slightly on a steam-bath. The aqueous solution was extracted with ether (4 x 50 ml.), and the ethereal solution was washed with saturated sodium bicarbonate (3 x 50 ml.) and with water until neutral. Drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation yielded a colourless gum which crystallised from methanol to yield 5-acetoxy-6-acetoxymethyl-7-methoxyphthalide (0.13 gm.; 47%) as needles, m.p. 90-91° (Found: C, 57.2; H, 5.0.  $\text{C}_{14}\text{H}_{14}\text{O}_7$  requires C, 57.1; H, 4.8%).

(b) 5-Hydroxy-6-hydroxymethyl-7-methoxyphthalide (0.26 g.) was dissolved in acetic anhydride (10 ml.) and concentrated sulphuric acid (1 drop) was added. The solution was heated on a steam-bath for 3 hr. and poured into water (150 ml.). The aqueous solution was heated to around 50° and on cooling was extracted with ether (3 x 50 ml.) and chloroform (2 x 50 ml.). The combined solvent extracts were washed with saturated sodium bicarbonate (4 x 50 ml.) and with water until neutral. Drying and evaporation of the solvent yielded a colourless gum which on recrystallisation from chloroform-ligroin gave 5-acetoxy-6-acetoxymethyl-7-

methoxyphthalide (0.25 g.; 69%) as needles, m.p. and mixed m.p. 90-91°.

The identical nature of the products from (a) and (b) was confirmed by comparison of the infrared spectra of the compounds in Nujol.

5-Hydroxy-7-methoxy-6-methylphthalide. - 5-Hydroxy-6-hydroxymethyl-7-methoxyphthalide (70 mg.) was dissolved in glacial acetic acid and shaken with hydrogen at atmospheric pressure and a temperature of 95° for 12 hr. in the presence of pre-reduced platinum catalyst (40 mg.). The catalyst was removed by filtration and washed with glacial acetic acid. The filtrate and washings were partially evaporated. Water (100 ml.) was added and the solution was extracted with ether (3 x 30 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 20 ml.) and with water until neutral. Drying and evaporation yielded a colourless gum which on recrystallisation from chloroform yielded 5-hydroxy-7-methoxy-6-methylphthalide (28 mg.; 43%) as felted needles, m.p. (in vacuo) 275° (decomp.) (Found: C, 61.8; H, 4.8.  $C_{10}H_{10}O_4$  requires C, 61.9; H, 5.2%).

Attempted Preparation of 5-Hydroxy-7-methoxy-6-methylphthalide. - (a) 5-Hydroxy-6-hydroxymethyl-7-methoxy-

phthalide (60 mg.) was dissolved in ethyl acetate and shaken with hydrogen at atmospheric pressure and room temperature for 20 hr. in the presence of pre-reduced Adams' catalyst (70 mg.). The catalyst was removed by filtration and washed with chloroform (3 x 20 ml.). The combined solution on evaporation gave white amorphous material which was recrystallised from acetone-benzene to yield unchanged material (50 mg.) as needles, m.p. 320°. The infrared spectrum of the product in Nujol was identical with that of the starting material.

(b) 5-Acetoxy-6-acetoxymethyl-7-methoxyphthalide (0.1 g.), dissolved in ethyl acetate (40 ml.), was shaken with hydrogen at room temperature and atmospheric pressure for 20 hr. in the presence of pre-reduced Adams' catalyst (80 mg.). The catalyst was removed by filtration and washed with chloroform (3 x 20 ml.). The filtrate and washings on removal of solvent yielded a colourless oil which on crystallisation from chloroform gave unchanged material (91 mg.).

(c) 5-Acetoxy-6-acetoxymethyl-7-methoxyphthalide (0.1 g.), dissolved in glacial acetic acid (45 ml.), was shaken with hydrogen at atmospheric pressure and a temperature of 95° for 20 hr. in the presence of pre-reduced Adams' catalyst

(80 mg.). The catalyst was removed by filtration and washed with glacial acetic acid. The filtrate and washings were partially evaporated. Water (100 ml.) was added and the solution was extracted with ether (3 x 30 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 20 ml.) and with water until neutral. Drying and evaporation yielded a colourless gum which gave unchanged 5-acetoxy-6-acetoxymethyl-7-methoxyphthalide (93 mg.) on recrystallisation from methanol.

The products from preparations (b) and (c) have infrared spectra in Nujol identical with that of the starting material.

5,7-Dimethoxy-6-hydroxymethylphthalide. - (a) 5-Hydroxy-6-hydroxymethyl-7-methoxyphthalide (70 mg.) was dissolved in ethanol (40 ml.) and treated with excess diazomethane in ether for 12 hr. The solvent and remaining diazomethane was removed by gentle heating under reduced pressure. The residual white solid was recrystallised from methanol to yield 5,7-dimethoxy-6-hydroxymethylphthalide (65 mg.; 87%) as needles, m.p. 175-176° (Found: C, 58.8; H, 5.6.  $C_{11}H_{12}O_5$  requires C, 58.9; H, 5.4%).

(b) 7-Hydroxy-6-hydroxymethyl-5-methoxyphthalide (80 mg.) was dissolved in ethanol (35 ml.) and treated with an

excess of diazomethane in ether for 12 hr. The solvent and remaining diazomethane was removed by gentle heating under reduced pressure. The residual white solid was recrystallised from methanol to yield 5,7-dimethoxy-6-hydroxymethylphthalide (78 mg.; 91.5%) as needles, m.p. and mixed m.p. 174-176°. The product obtained had an infrared spectrum in Nujol identical with that of the product from (a).

Attempted Preparation of Ethyl 3,6-Di(bromomethyl)-2,4-dimethoxybenzoate. - (a) Ethyl 3,6-di(bromomethyl)-4-hydroxy-2-methoxybenzoate (0.1 g.) was dissolved in ethanol (20 ml.) and treated with an excess of ethereal diazomethane for 24 hr. The solvent and remaining diazomethane was removed by gently heating the solution under reduced pressure. The remaining oil crystallised from ligroin to yield unchanged material (90 mg.).

(b) Ethyl 3,6-di(bromomethyl)-2-hydroxy-4-methoxybenzoate (0.1 g.) was dissolved in ethanol (30 ml.) and treated with an excess of ethereal diazomethane for 24 hr. The solvent and remaining diazomethane was removed by gently heating the solution under reduced pressure. The remaining oil crystallised from benzene-ligroin to yield unchanged material (95 mg.).

The products from preparations (a) and (b) were proved

identical with the starting material by mixed m.p. determination and infrared comparison in Nujol.

Tribromination of Ethyl 3,6-Dimethyl-4-hydroxy-2-methoxybenzoate. - Ethyl 3,6-dimethyl-4-hydroxy-2-methoxybenzoate (0.34 g.) was dissolved in dry carbon tetrachloride (100 ml.) in a quartz flask, heated and irradiated by 150 W. lamp. Bromine (0.74 g.  $\equiv$  3 mols.) in carbon tetrachloride (4.4 ml.) was added dropwise to the refluxing solution over a period of 5 hr. On evaporation of the solvent a dark brown gum was obtained which crystallised from cyclohexane in very low yield to give a tribromide (30 mg.; 4%) as prisms, m.p. 136-138° (Found: C, 32.3; H, 3.5; Br, 49.4.  $C_{12}H_{13}O_4Br_3$  requires C, 31.3; H, 2.8; Br, 52.0%). A brown oil (0.35 g.) was also obtained but could not be purified.

Attempted Hydrolysis of the Products of Tribromination. - (a) The solid tribromide (50 mg.), dissolved in acetone (50 ml.) and water (25 ml.), was refluxed on a mantle for 24 hr. The solvent was partially evaporated and the solution was allowed to cool. No separation of material took place. After dilution with water (50 ml.), ether extraction of the solution in the normal manner yielded a brown gum (45 mg.) which could not be crystallised.

(b) The brown oil (0.30 g.), dissolved in acetone (60 ml.) and water (30 ml.), was refluxed for 24 hr. By use of the experimental procedure employed in (a) a brown gum (0.22 g.) was obtained which could not be purified.

Attempted Dibromination of Ethyl 2,5-Dimethyl-4-ethoxycarbonyl-3-methoxyphenyl Carbonate and Subsequent Hydrolysis. - Ethyl 2,5-dimethyl-4-ethoxycarbonyl-3-methoxyphenyl carbonate as the redistilled oil (0.71 g.), was dissolved in dry carbon tetrachloride (50 ml.) in a quartz flask, heated and irradiated by a 150 W. lamp. Bromine (0.77 g.  $\approx$  2 mols.) in dry carbon tetrachloride (4.75 ml.) was added dropwise over a period of  $2\frac{1}{2}$  hr. On evaporation a brown gum (0.77 g.) was obtained which could not be obtained in a pure condition. This gum was dissolved in acetone (80 ml.) and water (40 ml.) and was refluxed for 24 hr. On partial evaporation no solid material separated. Dilution with water (100 ml.) and ether extraction yielded an uncrystallisable brown gum (0.65 g.).

Ethyl 4-Benzoyloxy-3,6-dimethyl-2-methoxybenzoate. - Ethyl 3,6-dimethyl-4-hydroxy-2-methoxybenzoate (0.75 g.), dissolved in pyridine (15 ml.), was treated with benzoyl chloride (0.7 g.) over a period of 10 minutes with shaking



and heated on a steam-bath for 4 hr. The solution was poured into water and the product was extracted with ether (3 x 30 ml.). The ethereal solution was washed with 1N. sodium hydroxide (3 x 20 ml.), with 6N. hydrochloric acid (3 x 15 ml.) and with water until neutral. Drying and evaporation yielded a colourless oil, crystallisation of which from methanol gave ethyl 4-benzoyloxy-3,6-dimethyl-2-methoxybenzoate (0.71 g.; 65%) as prisms, m.p. 67-68° (Found: C, 69.5; H, 6.3.  $C_{19}H_{20}O_5$  requires C, 69.5; H, 6.1%).

Ethyl 4-Benzoyloxy-3,6-di(bromomethyl)-2-methoxybenzoate. - Ethyl 4-benzoyloxy-3,6-dimethyl-2-methoxybenzoate (1.46 g.) was dissolved in dry carbon tetrachloride (200 ml.) in a quartz flask, heated and irradiated by a 150 W. lamp. Bromine (1.46 g.  $\equiv$  2 mols.), dissolved in carbon tetrachloride (9.0 ml.), was added dropwise to the refluxing solution over a period of  $1\frac{1}{2}$  hr. The solvent was removed and the residual gum on trituration with ligroin and subsequent recrystallisation from the same solvent gave ethyl 4-benzoyloxy-3,6-di(bromomethyl)-2-methoxybenzoate (1.04 g.; 48%) as plates, m.p. 99-100° (Found: C, 47.3; H, 3.9.  $C_{19}H_{18}O_5Br_2$  requires C, 47.0; H, 3.7%).

Methyl 2,4-Diacetoxy-3-diacetoxymethyl-6-methylbenzoate. - Methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (0.5 g.) was dissolved in acetic anhydride (17 ml.) containing concentrated sulphuric acid (1 drop) and heated on a steam-bath for  $2\frac{1}{2}$  hr. The solution was poured into water and the product was extracted with ether (4 x 40 ml.). The ethereal solution was washed by saturated sodium bicarbonate (4 x 25 ml.) and with water (3 x 30 ml.). Drying and removal of solvent under reduced pressure gave a colourless gum which on recrystallisation from chloroform-ligroin yielded methyl 2,4-diacetoxy-3-diacetoxymethyl-6-methylbenzoate (0.5 g.; 75%) as prisms, m.p. 126-127° (Found: C, 54.4; H, 5.2.  $C_{18}H_{20}O_{10}$  requires C, 54.5; H, 5.1%).

Attempted Preparation of Methyl 4-Acetoxy-2-benzyloxy-3-formyl-6-methylbenzoate. - Methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (0.2 g.), dissolved in acetic anhydride (5 ml.) and pyridine (5 ml.), was heated on a steam-bath for 3 hr. The reaction mixture was poured into water and was allowed to stand overnight. The aqueous suspension was extracted with ether (3 x 50 ml.). The ethereal solution was washed with 1N. sodium hydroxide (3 x 40 ml.), with 6N. hydrochloric acid (2 x 30 ml.) and with water. On drying ( $Na_2SO_4$ ) and removal of solvent under

reduced pressure no product was obtained. The alkaline wash liquors were acidified with dilute hydrochloric acid and extracted with ether (3 x 50 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 30 ml.) and with water until neutral. On evaporation of the dried solution a brown gum was obtained which crystallised from ethanol to yield unchanged methyl-2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (0.19 g.). The product and starting material had identical infrared spectra in Nujol.

Methyl 4-Benzoyloxy-2-benzyloxy-3-formyl-6-methylbenzoate. - Methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate (1 g.) was dissolved in pyridine (20 ml.) and benzoyl chloride (0.55 g.) was added in portions with shaking over 10 min. The mixture was heated on a steam-bath for 30 min. and after standing overnight at room temperature, was poured into water. The product was extracted with ether (3 x 40 ml.) and the ethereal solution was shaken with 1N. sodium hydroxide (6 x 30 ml.), with 2N. hydrochloric acid (6 x 10 ml.) and finally with water until neutral. Drying and removal of solvent under reduced pressure yielded a colourless gum which separated as crystals from acetone on cooling. Recrystallisation

from methanol gave methyl 4-benzoyloxy-2-benzyloxy-3-formyl-6-methylbenzoate (0.9 g.; 67%) as prisms, m.p. 94-96° (Found: C, 71.2; H, 5.2.  $C_{24}H_{20}O_6$  requires C, 71.2; H, 5.0%).

Attempted Preparation of Methyl 4-Benzoyloxy-3,6-dimethyl-2-hydroxybenzoate. - (a) Methyl 4-benzoyloxy-2-benzyloxy-3-formyl-6-methylbenzoate (0.26 g.), dissolved in dry ethyl acetate (45 ml.), was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure in the presence of palladised charcoal (20% Pd) for 12 hr. The catalyst was removed by filtration and thoroughly washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness. The residual white solid was recrystallised from methanol and gave unchanged methyl 4-benzoyloxy-2-benzyloxy-3-formyl-6-methylbenzoate (0.23 g.). The product was confirmed to be unchanged starting material by comparison of infrared spectra in Nujol and mixed m.p. determination.

(b) Methyl 4-benzoyloxy-2-benzyloxy-3-formyl-6-methylbenzoate (0.20 g.), dissolved in glacial acetic acid (40 ml.), was shaken in an atmosphere of hydrogen at atmospheric pressure and a temperature of 95° in the presence of pre-reduced Adams' catalyst for 10 hr. The catalyst was

removed by filtration and washed with glacial acetic acid (3 x 20 ml.). The filtrate and washings were evaporated to small volume (c. 5 ml.). Water (100 ml.) was added and the suspension was extracted with ether (3 x 30 ml.). The ethereal solution was washed with saturated sodium bicarbonate solution (3 x 20 ml.) and shaken with 1N. sodium hydroxide (3 x 20 ml.). The alkaline solution was acidified and extracted with ether (3 x 20 ml.). The ethereal solution was washed with saturated sodium bicarbonate (3 x 10 ml.) and with water until neutral. Drying and evaporation of the solvent yielded no product. The original ethereal solution yielded a brown oil (0.15 g.) which could not be crystallised.

The experiment was repeated with a reaction time of 18 hr. An uncrystallisable brown oil was obtained once more from the neutral fraction.

Attempted Preparation of Methyl 4-Benzoyloxy-3-formyl-2-hydroxy-6-methylbenzoate. - Methyl 4-benzoyloxy-2-benzyloxy-3-formyl-6-methylbenzoate (0.25 g.), dissolved in glacial acetic acid (15 ml.), was treated with concentrated hydrochloric acid (saturated with hydrogen chloride gas at 0°) (6 ml.). The solution was heated on a steam-bath for 35 min. The solvent was removed and the residue was

dissolved in ether (300 ml.). The ethereal solution was shaken with 1N. sodium hydroxide (4 x 50 ml.) and the alkaline solution was acidified. The solid material which separated was collected. Recrystallisation from methanol yielded methyl haematommate (0.12 g.; 92%). The infrared spectra in Nujol of the product and of the authentic methyl haematommate were identical and a mixed m.p. determination gave no depression.

Attempted Preparation of 3,5-Dihydroxybenzyl Alcohol. -

(a) 3,5-Dihydroxybenzoic acid<sup>59</sup> (1.29 g.), dissolved in dry tetrahydrofuran (40 ml.), was quickly added to lithium aluminium hydride (1.39 g.) in dry tetrahydrofuran (120 ml.) contained in a 3-necked flask, fitted with a condenser and stirrer and protected from atmospheric moisture. The mixture was boiled under reflux for  $3\frac{1}{2}$  hr. with stirring on a steam-bath. Water (2 ml.) was then added dropwise until effervescence ceased. Addition of dilute sulphuric acid (15% v/v; 50 ml.) brought about the separation of a gummy solid which redissolved on further addition of water (200 ml.). The aqueous tetrahydrofuran solution was shaken with ether (6 x 250 ml.) and chloroform (2 x 250 ml.). The combined organic solutions were shaken with saturated sodium hydrogen carbonate (3 x 100 ml.) and with water until

neutral. On drying the solution and removing the solvent under reduced pressure no product was obtained.

Acidification of the alkaline solution and ether extraction yielded unchanged 3,5-dihydroxybenzoic acid (1.20 g.).

(b) 3,5-Dihydroxybenzoic acid (1.29 g.), dissolved in dry tetrahydrofuran (120 ml.), was added quickly to lithium aluminium hydride (1.39 g.) in dry tetrahydrofuran (600 ml.), contained in a 3-necked flask fitted up as in (a). Subsequently a similar experimental procedure to that of (a) was employed, but no neutral product was obtained. 3,5-Dihydroxybenzoic acid (1.12 g.) was isolated from the acidic fraction.

(c) 3,5-Dihydroxybenzoic acid (1 g.) was dissolved in dry ether (50 ml.) and was added quickly to lithium aluminium hydride (1 g.) in dry ether (500 ml.) in a 3-necked flask fitted up as in (a). The mixture was refluxed for 3 hr. with stirring on a steam-bath and the excess lithium aluminium hydride was destroyed by dropwise addition of water. Concentrated sulphuric acid (3 ml.) in water (50 ml.) was added, followed by water (200 ml.). The ethereal layer was separated and the aqueous phase was extracted with ether (3 x 100 ml.) and chloroform (2 x 100 ml.). The combined solutions were washed with

saturated sodium bicarbonate solution (5 x 50 ml.) and with water until neutral. No product was obtained on evaporation of the dried solution. Acidification and ether extraction of the alkaline washes yielded 3,5-dihydroxybenzoic acid (0.91 g.) unchanged.

The products from preparations (a), (b) and (c) had infrared spectra in Nujol identical with that of the starting material.

(d) Methyl 3,5-dihydroxybenzoate<sup>61</sup> (1 g.), dissolved in dry ether (50 ml.), was added to a suspension of lithium aluminium hydride (1 g.) in dry ether (500 ml.) in the 3-necked flask fitted up as previously described. The suspension was stirred under reflux on a steam-bath for 4 hr. Water (2 ml.) was added dropwise followed by concentrated sulphuric acid (5 ml.) in water (200 ml.). The phases were separated and the aqueous phase was extracted with ether (3 x 100 ml.) and chloroform (2 x 50 ml.). The combined organic solutions were then shaken with saturated sodium bicarbonate (3 x 50 ml.) and with water until neutral. Removal of the solvent under reduced pressure from the dried solution yielded a brown residue which from acetone-chloroform gave unchanged material (0.91 g.). The product and starting material had identical infrared spectra in Nujol.



(e) 3,5-Diacetoxybenzoic acid<sup>62</sup> (0.8 g.), dissolved in dry ether (150 ml.), was added in small portions to a 3-necked flask, fitted up as in (a), containing lithium aluminium hydride (0.97 g.) in dry ether (300 ml.). The mixture was refluxed with stirring on a steam-bath for 4 hr. Water (3 ml.) was added dropwise, followed by concentrated sulphuric acid (5 ml.) in water (200 ml.). The ethereal layer was separated and the aqueous phase was extracted with ether (3 x 100 ml.) and chloroform (2 x 100 ml.). The combined solutions were washed with saturated sodium bicarbonate (4 x 50 ml.) and with water until neutral. Evaporation of the dried solution yielded no product. Acidification of the bicarbonate solution and ether extraction in the normal manner yielded 3,5-dihydroxybenzoic acid (0.75 g.), m.p. 236-238° (lit.,<sup>59</sup> m.p. 235°). The product was confirmed to be 3,5-dihydroxybenzoic acid by mixed m.p. determination and comparison of infrared spectra in Nujol.

(f) 3,5-Diacetoxybenzoic acid (0.50 g.) was slowly added with stirring to sodium borohydride (0.93 g.) and bis(2-methoxyethyl) ether (48 ml.) in a nitrogen atmosphere. Boron trifluoride etherate (4.65 g.) in bis(2-methoxyethyl) ether (25 ml.) was added over a period of 1 hr. whilst the mixture was stirred at room temperature. After 2 hr.

bis(2-methoxyethyl)ether (50 ml.) was added. The reaction was allowed to stand overnight and destroyed by ice (3 g.) in methanol (10 ml.). The reaction mixture was poured into water (100 ml.) and extracted with ether (5 x 20 ml.). The ethereal solution was washed with sodium bicarbonate solution (5 x 10 ml.) and with water until neutral. Drying and evaporation of the solvent under reduced pressure gave no product.

Ether extraction of the acidified alkaline washings gave 3,5-dihydroxybenzoic acid (0.23 g.) identified as before by mixed m.p. and comparison of infrared spectra in Nujol.

(g) Methyl 3,5-diacetoxybenzoate<sup>63</sup> (1.17 g.), dissolved in dry ether (130 ml.), was added to lithium aluminium hydride (1.5 g.) in boiling ether (130 ml.) in a 3-necked flask, fitted up as previously described. The mixture was refluxed for  $3\frac{1}{2}$  hr. on a steam-bath with stirring. Water (3 ml.) was cautiously added dropwise followed by concentrated sulphuric acid (5 ml.) in water (200 ml.). The aqueous phase was extracted with ether (3 x 20 ml.) and the combined solutions were shaken with saturated sodium bicarbonate (3 x 15 ml.) and water until neutral. Evaporation of the dried solution yielded a brown gum which crystallised from acetone-chloroform to give methyl 3,5-dihydroxybenzoate (0.70 g.) as prisms, m.p. and mixed m.p.

164-166°. The product had an infrared spectrum in Nujol identical with that of methyl 3,5-dihydroxybenzoate.

(h) 3,5-Dimethoxybenzyl alcohol<sup>64,65</sup> (0.2 g.) was dissolved in acetic acid (8 ml.) and treated with hydrobromic acid (3 ml.; s.g. 1.49). The solution was heated on a steam-bath in an atmosphere of nitrogen for 20 min., was diluted with water (100 ml.) and was extracted with ether (4 x 20 ml.). The ethereal solution was washed with saturated sodium bicarbonate (4 x 15 ml.) and shaken with 1N. sodium hydroxide (6 x 10 ml.). The alkaline solution was acidified and extracted with ether to yield a brown gum (0.14 g.) which could not be crystallised.

(i) 3,5-Dimethoxybenzyl alcohol (1 g.) was dissolved in dry benzene (10 ml.) and added to a suspension of aluminium bromide (3.16 g.) in benzene (100 ml.). The mixture was refluxed in an atmosphere of nitrogen for 6½ hr. on a steam-bath. Water (150 ml.) was added, dropwise initially, and the benzene phase was separated from the aqueous. The aqueous phase was extracted with ether (3 x 50 ml.) and the organic solutions were combined and shaken with 1N. sodium hydroxide (4 x 25 ml.). The alkaline solution was acidified and extracted with ether in the normal manner to yield a brown gum (0.82 g.) which could not be crystallised.

Methyl 3,5-Diacetoxybenzoate. - 3,5-Diacetoxybenzoic acid (1.0 g.) was dissolved in methanol (10 ml.) and treated for 2 hr. with excess ethereal diazomethane. The solvent and unreacted diazomethane was boiled off carefully. The residual oil was dissolved in ether (50 ml.) and the ethereal solution was washed with saturated sodium bicarbonate (3 x 15 ml.) and with water until neutral. On evaporation of the dried solution a colourless oil was obtained which crystallised from ligroin to yield methyl 3,5-diacetoxybenzoate (0.69 g., 67%) as needles, m.p. 58-59° (lit.,<sup>63</sup> m.p. 58-59°) (Found: C, 57.5; H, 4.7. Calc. for  $C_{12}H_{12}O_6$ : C, 57.1; H, 4.8%).

Attempted Preparation of Methyl 3,5-Diacetoxybenzoate. - 3,5- Diacetoxybenzoic acid (1 g.) was dissolved in methanol (25 ml.) and concentrated sulphuric acid (2 ml.) was added. The solution was refluxed for 6 hr. on a steam-bath, diluted by water (200 ml.) and extracted with ether (4 x 30 ml.). The ether solution was washed with saturated sodium bicarbonate (4 x 20 ml.) and with water until neutral. Removal of the dried solvent under reduced pressure yielded a white solid which on recrystallisation from benzene gave methyl 3,5-dihydroxybenzoate (0.56 g.) as prisms, m.p. and mixed m.p. 164-166° (lit.,<sup>61</sup> m.p. 162-165°).

The product and authentic methyl 3,5-dihydroxybenzoate had identical infrared spectra in Nujol.

Attempted Preparation of 3,5-Dibenzyloxybenzoic Acid. -

(a) 3,5-Dihydroxybenzoic acid (1.14 g.) was dissolved in acetone (80 ml.) and refluxed with potassium carbonate (1.28 g.) and benzyl chloride (3.72 g.) for 12 hr. The acetone was removed by evaporation and the organic residue was dissolved in ether (50 ml.). The ethereal solution was extracted with saturated sodium bicarbonate (3 x 20 ml.). The alkaline solution was acidified and re-extracted with ether to yield 3,5-dihydroxybenzoic acid (1.10 g.) unchanged.

(b) 3,5-Dihydroxybenzoic acid (1.75 g.) was dissolved in dioxan (120 ml.) containing potassium carbonate (1.95 g.) and benzyl chloride (5.72 g.) and the mixture was refluxed for 30 hr. The dioxan was removed by evaporation and the organic residue was dissolved in ether (50 ml.). The ethereal solution was shaken with saturated sodium bicarbonate (4 x 20 ml.). The alkaline solution was acidified and re-extracted with ether to yield 3,5-dihydroxybenzoic acid (1.67 g.) unchanged. Product and starting material had identical infrared spectrum in Nujol in both experiments.

## B I B L I O G R A P H Y

1. Fritsch, Ann., 1897, 296, 344;  
1898, 301, 352.
2. Nikuni, J. Agr. Chem. Soc. Japan,  
1938, 14, 352.
3. Haber, Nikuni, Schmid  
and Yagi, Helv. Chim. Acta, 1956,  
39, 1654.
4. Horii and Tanaka, Chem. and Ind., 1959, 1576.
5. Horii, Katagi and Tamura, ibid., 1960, 1088.
6. Vrškóc, Herout and Sörm, Coll. Chim. Czeck.,  
1959, 24, 3938.
7. Allison and Newbold, J. Chem. Soc., 1959, 3335.
8. Asahina and Shibata, 'Chemistry of Lichen  
Substances', Japan Society  
for the Promotion of Science,  
Tokyo, 1954, p. 124.
9. op. cit., p. 130.
10. op. cit., pp. 134 and 137.
11. op. cit., p. 170.
12. op. cit., p. 120 et seq.
13. Birkinshaw, Raistrick  
and Ross, Biochem. J., 1952, 50, 630.
14. Birkinshaw, Raistrick,  
Ross and Stickings, ibid., p. 610.
15. Senkhaka, J. Sci. Ind. Res. (India),  
1957, 16c, 118.
16. Brian, Curtis, Grove,  
Hemming and McGowan, Nature, 1946, 157, 697.
17. Raistrick and Ross, Biochem J., 1952, 50, 635.

18. Manske and Holmes, 'The Alkaloids', Academic Press, New York, 1954, Vol. IV, p. 167.
19. Pasternack, Bayley, Wagner, Hochstein, Regna and Brunings, J. Amer. Chem. Soc., 1952, 74, 1926.
20. Hutchings, Waller, Gordon, Broschard, Wolff, Goldman and Williams, J. Amer. Chem. Soc., 1952, 74, 3710.
21. Duncanson, Grove and Zealley, J. Chem. Soc., 1953, 3637.
22. Grove, Biochem. J., 1952, 50, 648.
23. Grove and Willis, J. Chem. Soc., 1951, 877.
24. Grove, ibid., 1952, 3345.
25. idem, Biochem. J., 1953, 54, 664.
26. Brown and Newbold, J. Chem. Soc., 1953, 1285.
27. idem, ibid., p. 3648.
28. idem, ibid., 1954, 1076.
29. Blair, Logan and Newbold, ibid., 1956, 2443.
30. Elderfield, 'Heterocyclic Compounds', Chapman-Hall, London, Vol. II, p. 92 et seq.
31. Edwards, Perkin and Stoyale, J. Chem. Soc., 1925, 195.
32. Charlesworth, Rennie, Sinder and Yan, Canadian J. Res., 1945, 23B, 17.
33. Mermod and Simonis, Ber., 1908, 41, 983.
34. Simonis, Marben and Mermod, Ber., 1905, 38, 3981.



35. Simonis and Arand, Ber., 1909, 42, 3726.
36. Eliel and Rivard, J. Org. Chem., 1952, 17, 1252.
37. Eliel, Burgstahler and Rivard, ibid., 1953, 18, 1679.
38. Colson and Gautier, Ann. chim., 1887 (6) 11, 29.
39. Fuson, J. Amer. Chem. Soc., 1926, 48, 1093.
40. Brewster, ibid., 1918, 40, 406.
41. Segesser and Calvin, ibid., 1942, 64, 825.
42. Ross, Markarian, Young and Nazzewski, ibid., 1950, 72, 1133.
43. Sampey and Reid, ibid., 1947, 69, 234.
44. Coleman and Honeywell, Org. Syntheses, Coll. Vol. II, 1943, 89.
45. idem, ibid., p. 89, footnote 6.
46. Cummings, Hopper and Wheeler, 'Systematic Organic Chemistry', Constable, London, 1950, p. 358.
47. Logan and Newbold, J. Chem. Soc., 1957, 1946.
48. Duncanson, Grove and Zealley, ibid., 1953, 1331.
49. Bellamy, 'The Infrared Spectra of Complex Molecules', Methuen, London, 2nd Edition, p. 179 et seq.
50. Pauling, 'Nature of the Chemical Bond', Oxford University Press, London, 2nd Edition, p. 289.

51. Schilling and Vorlander, Ann., 1899, 308, 195.
52. St. Pfau, Helv. Chim. Acta, 1933, 16,  
282.
53. Fischer and Hoesch, Ann., 1912, 391, 347.
54. Whalley, J. Chem. Soc., 1949, 3278.
55. Sonn, Ber., 1929, 62, 3012.
56. Robertson and Stephenson, J. Chem. Soc., 1930, 313.
57. idem, ibid., 1932, 1675.
58. Asahina and Simusato, Ber., 1938, 71, 2561.
59. Weston and Suter, Org. Syntheses, Coll. Vol. III,  
1955, p. 288.
60. Hargreaves, Chem. and Ind., 1954, 578.
61. Herzig and Epstein, Monatsh., 1908, 29, 668.
62. Kloetzel and Abadir, J. Amer. Chem. Soc.,  
1955, 77, 3823.
63. Mody and Shah, Proc. Indian Acad. Sci.,  
1951, 34A, 77.
64. Bülow and Riess, Ber., 1902, 35, 3901.
65. Adams, Harfenist and  
Loewe, J. Amer. Chem. Soc., 1949,  
71, 1624.
66. Burwell, Chem. Revs., 1954, 615.
67. Smith and Stephen, Tetrahedron Letters, 1960,  
7, 17.
68. Pauling, J. Amer. Chem. Soc.,  
1936, 58, 94.

## APPENDIX

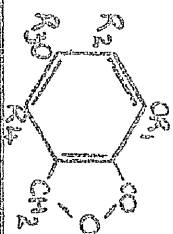


Table I. Ultraviolet and Infrared Data on Phthalide Derivatives

(v)

	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	$\lambda_{\text{max}}^{\text{A}}$ max [mμ]	$\nu_{\text{max}}$ [cm. <sup>-1</sup> ] in Nujol	Band * Assignment	$\nu_{\text{max}}$ [cm. <sup>-1</sup> ] in Chloroform	Band Assignment
LXXVI	CH <sub>3</sub>	H	H	Br	216[ $\leq$ 412, 400] 241[ $\leq$ 9, 100] 304[ $\leq$ 11, 400]	1721		1751	Phthalide carbonyl
LI	CH <sub>3</sub>	H	CH <sub>3</sub>	Br	220[ $\leq$ 34, 000] 259[ $\leq$ 12, 000] 298[ $\leq$ 7, 100]	1757	Phthalide carbonyl	1764	Phthalide carbonyl
LXXVII	CH <sub>3</sub>	H	Ac	Br	214[ $\leq$ 42, 300] 240[ $\leq$ 11, 900] 300[ $\leq$ 5, 600]	1748 1778	Phthalide carbonyl 'Phenolic' acetate	1754[broad]	Incompletely resolved
LXXVIII	CH <sub>3</sub>	H	Ac	H	214[ $\leq$ 18, 800] 242[ $\leq$ 10, 200] 290[ $\leq$ 5, 000]	1765 [broad]	Incompletely resolved	1755[broad]	Incompletely resolved
LXVI	CH <sub>3</sub>	H	H	H	216[ $\leq$ 27, 700] 236[ $\leq$ 15, 600] 287[ $\leq$ 5, 000]	1724		1764	Phthalide carbonyl
XLVIII	CH <sub>3</sub>	H	CH <sub>3</sub>	H	216[ $\leq$ 37, 500] 256[ $\leq$ 16, 000] 290[ $\leq$ 5, 500]	1751	Phthalide carbonyl	1751	Phthalide carbonyl
LXXVIII	H	CH <sub>2</sub> OH	CH <sub>3</sub>	H	222[ $\leq$ 34, 100] 268[ $\leq$ 21, 600] 305[ $\leq$ 5, 800]	1736	H-bonded Phthalide carbonyl	1736	H-bonded Phthalide carbonyl
CVII	CH <sub>3</sub>	CH <sub>2</sub> OH	CH <sub>3</sub>	H	220[ $\leq$ 35, 300] 258[ $\leq$ 24, 600]	1764	Phthalide carbonyl	1767	Phthalide carbonyl

Table I (Continued)

XO	Ac	CH <sub>2</sub> OAc	CH <sub>3</sub>	H	214[ $\leq$ 46,400] 254[ $\leq$ 13,400]	1783 1754	Phenolic acetate Phthalide carbonyl	1776 [broad]	Incompletely resolved
XOI	H	CH <sub>2</sub> OCH <sub>3</sub>	CH <sub>3</sub>	H	218[ $\leq$ 29,400] 270[ $\leq$ 18,300] 302[ $\leq$ 7,500]	1739	H-bonded Phthalide carbonyl	1736	H-bonded Phthalide carbonyl
OIV	CH <sub>3</sub>	CH <sub>2</sub> OH	H	H	222[ $\leq$ 20,000] 264[ $\leq$ 12,600]	1724		1767	Phthalide carbonyl
OV	CH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	H	H	218[ $\leq$ 33,700] 260[ $\leq$ 14,500]	1721		1761	Phthalide carbonyl
OVI	CH <sub>3</sub>	CH <sub>2</sub> OAc	Ac	H	214[ $\leq$ 46,400] 254[ $\leq$ 13,400]	1783 1751	Phenolic acetate Phthalide carbonyl	1776 [broad]	Incompletely resolved
OXII	CH <sub>3</sub>	CH <sub>2</sub> OH	Bz	H	216[ $\leq$ 41,900] 256[ $\leq$ 7,200]	1760 [broad]	2. completely resolved	1760 [broad]	Incompletely resolved
IXXA	CH <sub>3</sub>	CH <sub>3</sub>	H	H	212[ $\leq$ 50,100] 256[ $\leq$ 24,700]	1721		1758	Phthalide carbonyl

\* No assignment has been given to absorption bands detected in Nujol where intermolecular hydrogen bonding has taken place.

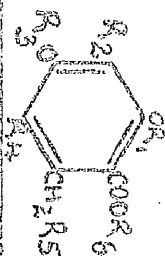


Table II Ultraviolet and Infrared Absorption Data on Esters

(VII)

	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	$\lambda$ max. [m $\mu$ ]	$\nu$ max. [cm. <sup>-1</sup> ] in Nujol	Band Assignment	$\nu$ max. [cm. <sup>-1</sup> ] in Chloro- form	Band Assignment
LXIX	H	H	CH <sub>2</sub> O.CO	H	H	CH <sub>3</sub>	220 [ε 25,000] 258 [ε 16,100] 306 [ε 3,100]	1764 1667	Carbonate H-bonded ester carbonyl	1773 1657	Carbonate H-bonded ester carbonyl
LXX	CH <sub>3</sub>	H	CH <sub>2</sub> O.CO	H	H	CH <sub>3</sub>	210 [ε 30,600] 246 [ε 20,200] 288 [ε 11,600]	1761 1730	Carbonate Ester carbonyl	1767 1733	Carbonate Ester carbonyl
LXXI	CH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	210 [ε 23,200] 250 [ε 4,800] 281 [ε 2,500]	1689		1721	Ester carbonyl
LXXII	CH <sub>3</sub>	H	H	Br	H	CH <sub>3</sub>	214 [ε 31,700] 288 [ε 3,000]	1695		1724	Ester carbonyl
LXXIII	CH <sub>3</sub>	H	CH <sub>3</sub>	Br	H	CH <sub>3</sub>	206 [ε 29,800] 289 [ε 3,300]	1721	Ester carbonyl	1724	Ester carbonyl
LXXIV	CH <sub>3</sub>	H	H	Br	Br	CH <sub>3</sub>	216 [ε 18,200] 310 [ε 3,400]	1709		1721	Ester carbonyl
LXXV	H	H	H	H	H	O <sub>2</sub> H <sub>5</sub>	216 [ε 24,700] 264 [ε 18,600] 300 [ε 6,000]	1647	H-bonded ester carbonyl	1656	H-bonded ester carbonyl
LXXVI	H	CHO	H	H	H	O <sub>2</sub> H <sub>5</sub>	204 [ε 16,700] 241 [ε 24,200] 260 [ε 18,200] 356 [ε 4,800]	1653 [broad]	Incompletely resolved	1650	H-bonded aromatic aldehyde carbonyl
LXXVII	H	CH <sub>3</sub>	H	H	H	O <sub>2</sub> H <sub>5</sub>	218 [ε 21,000] 270 [ε 13,900]	1653	H-bonded ester carbonyl	1656	H-bonded ester carbonyl



Table II (Continued)

O	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> .O.CO	H	H	C <sub>2</sub> H <sub>5</sub>	214[ $\leq$ 31,400] 250[ $\leq$ 31,000] 310[ $\leq$ 4,700]	1767 1667	Carbonate H-bonded ester carbonyl	1770 1661	Carbonate H-bonded ester carbonyl
CI	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> .O.CO	H	H	C <sub>2</sub> H <sub>5</sub>	214[ $\leq$ 29,200] 246[ $\leq$ 10,700] 284[ $\leq$ 3,900]			1767 [liquid] 1730 [liquid]	Carbonate
CII	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	C <sub>2</sub> H <sub>5</sub>	215[ $\leq$ 8,000] 250[ $\leq$ 2,300]	1683		1730	Ester carbonyl
CIII	CH <sub>3</sub>	CH <sub>2</sub> Br	H	H	Br	C <sub>2</sub> H <sub>5</sub>	218[ $\leq$ 20,200] 245[ $\leq$ 15,100] 278[ $\leq$ 12,200]	1701		1721	Ester carbonyl
CK	CH <sub>3</sub>	CH <sub>3</sub>	Bz	H	H	C <sub>2</sub> H <sub>5</sub>	210[ $\leq$ 21,100] 232[ $\leq$ 22,000]	1751	'Phenolic' benzoate	1748	'Phenolic' benzoate
OXI	CH <sub>3</sub>	CH <sub>2</sub> Br	Bz	H	Br	C <sub>2</sub> H <sub>5</sub>	212[ $\leq$ 29,800] 234[ $\leq$ 33,500]	1754	'Phenolic' benzoate	1754	'Phenolic' benzoate
OXII	Ac	AcO > CH	Ac	H	H	CH <sub>3</sub>	208[ $\leq$ 31,500]	1799	Diacetoxymethyl	1795	Diacetoxymethyl
OXIII								1773	'Phenolic' acetate	1770	'Phenolic' acetate
OXIV	C <sub>2</sub> H <sub>5</sub> .OH <sub>2</sub>	CHO	Bz	H	H	CH <sub>3</sub>	222[ $\leq$ 30,700] 302[ $\leq$ 3,400]	1754	'Phenolic' benzoate	1757	'Phenolic' benzoate
								1735	Ester carbonyl	1736	Ester carbonyl
								1695	Aromatic aldehyde carbonyl	1692	Aromatic aldehyde carbonyl



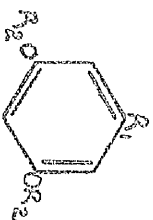


Table III. Ultraviolet and Infrared Data on Acids and Esters in the 2,6-Dibenzoyl Acid Series

	R <sub>1</sub>	R <sub>2</sub>	$\lambda$ max. (m $\mu$ )	$\nu$ max. [cm. <sup>-1</sup> ] in Nujol	Band Assignment	$\nu$ max. [cm. <sup>-1</sup> ] in chloroform	Band Assignment
XXVIII	COOH	H	212 [332,000] 242 [311,200] 310 [5,400]	1683	Carboxylic acid carbonyl	1686	Carboxylic acid carbonyl
XXIX	COOCH <sub>3</sub>	H	206 [20,400] 236 [9,100] 296 [6,200]	1695	H-bonded ester carbonyl	1695	H-bonded ester carbonyl
XXXI	COOH	Ac	208 [12,100] 278 [800]	1773	'Phenolic' acetate carbonyl	1779	'Phenolic' acetate carbonyl
XXXII	COOCH <sub>3</sub>	Ac	210 [14,700] 254 [11,100] 300 [3,000]	1783 1730	'Phenolic' acetate ester carbonyl	1786 1727	'Phenolic' acetate ester carbonyl
XXXIII	COOH	CH <sub>3</sub>	211 [21,700] 246 [5,200] 302 [2,800]	1686	Carboxylic acid carbonyl	1689	Carboxylic acid carbonyl
XXXIV	CH <sub>2</sub> OH	CH <sub>3</sub>	210 [15,100] 220 [6,200] 278 [1,900]			3448	'Phenolic'-OH